Focusing on the Use of GLP-1s in Treating MASH & Fatty Liver Disease

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GLP-1 Based Therapeutics Summit
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Forward-looking statements

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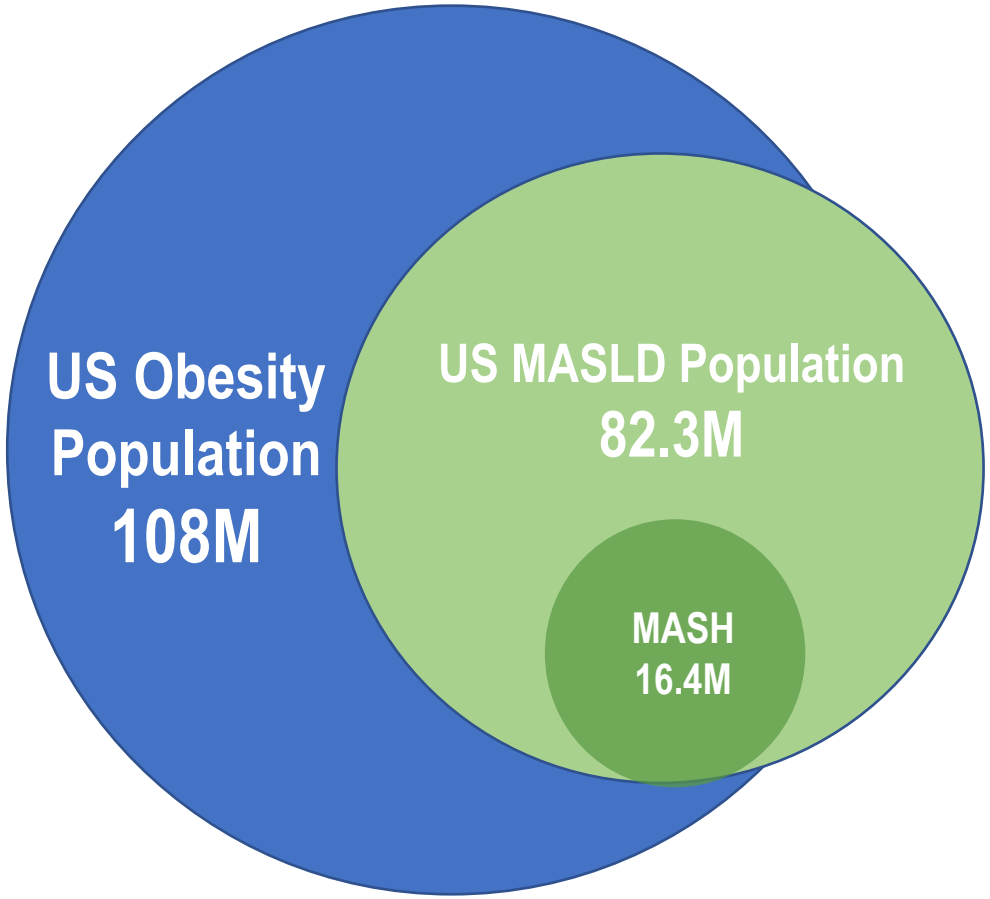
OBESITY AND FATTY LIVER DISEASE

DISEASES WITH UNMET NEED APPROACHING EPIDEMIC PROPORTIONS



The recent successes of semaglutide (Wegovy®) and tirzepatide (Mounjaro®) 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)

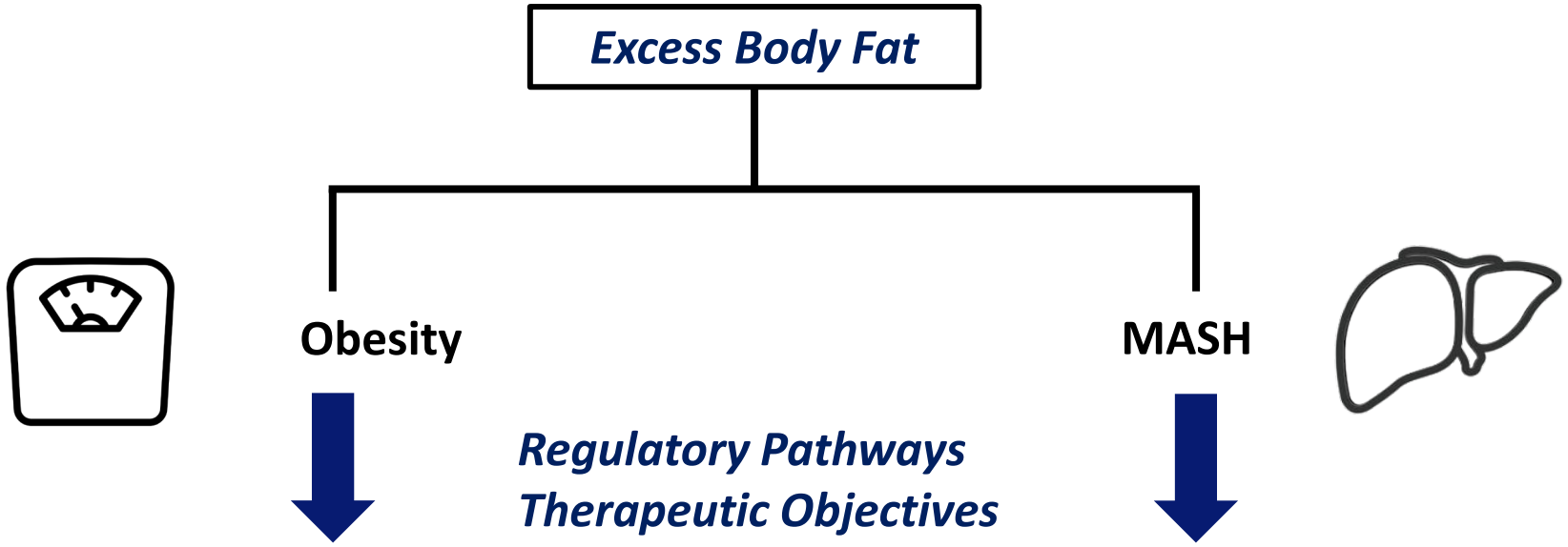
619 patients with biopsy confirmed MASH

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

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

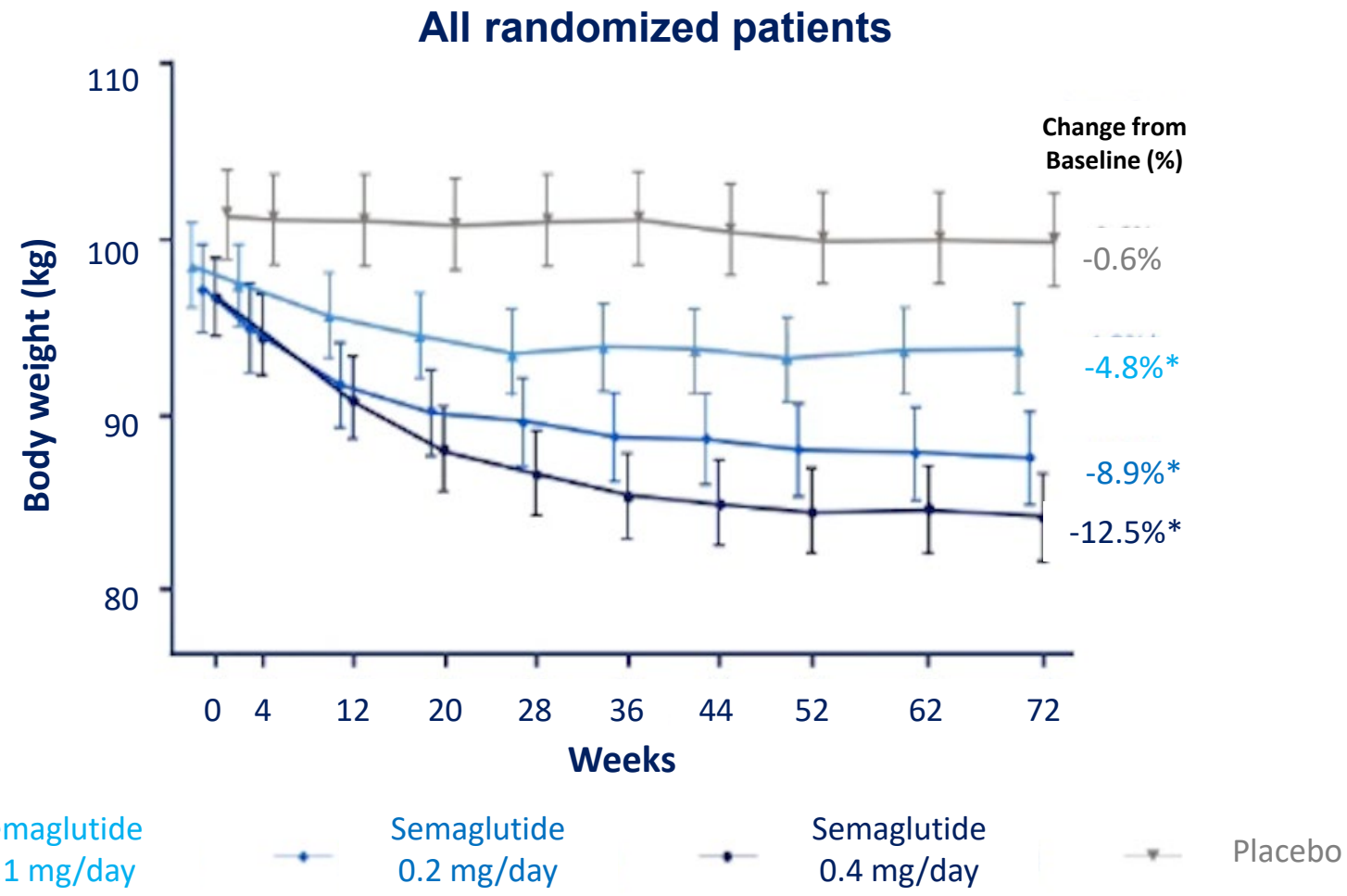
SNAPSHOT OF COMPOUNDS IN ADVANCED MASH DEVELOPMENT

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
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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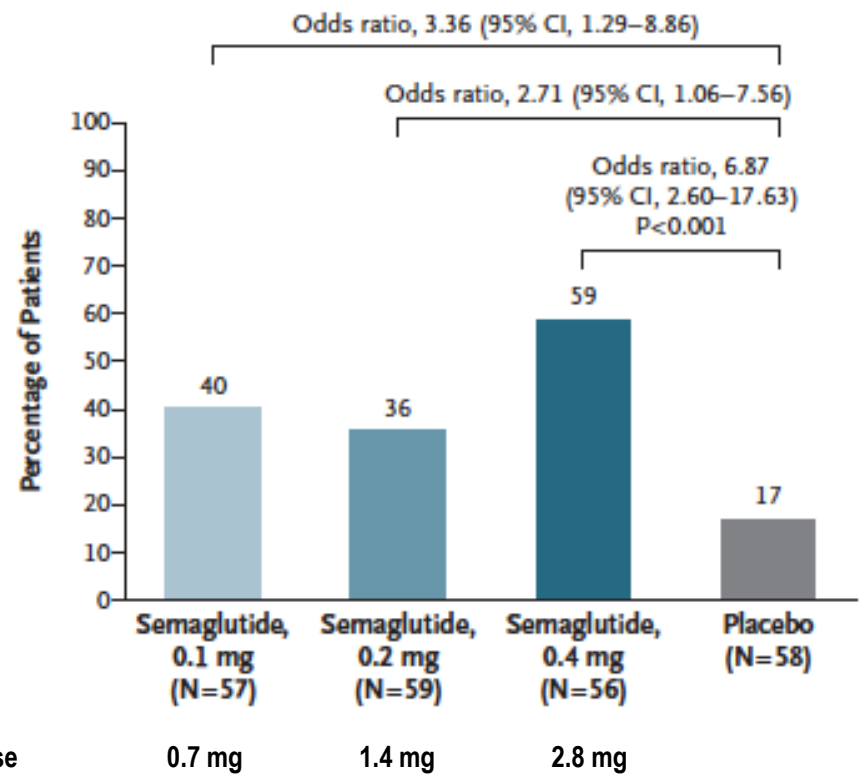
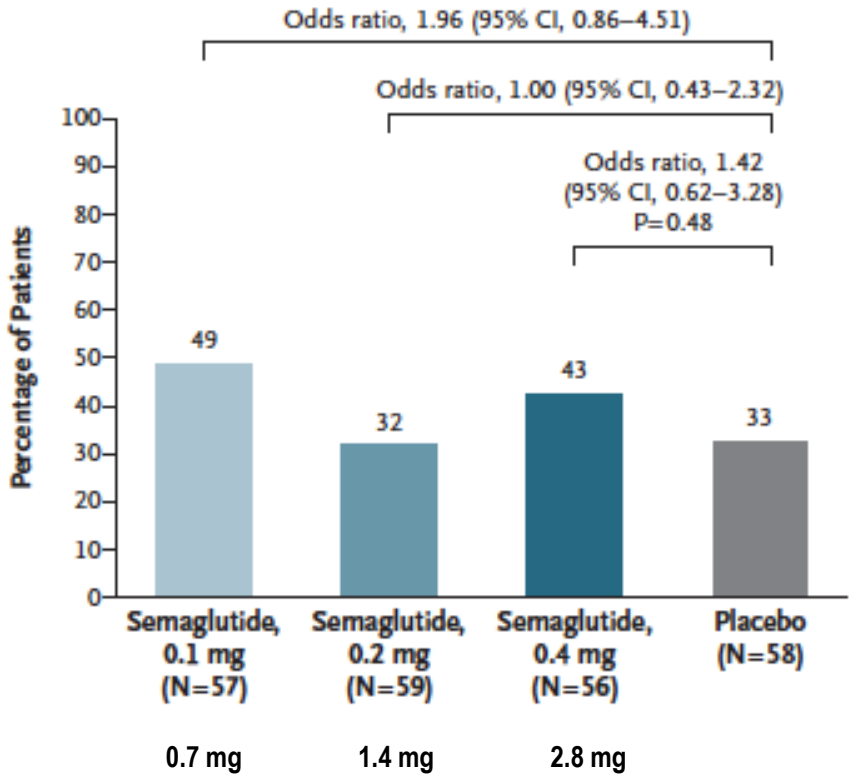
SEMAGLUTIDE—MASH RESOLUTION WITHOUT FIBROSIS IMPROVEMENT

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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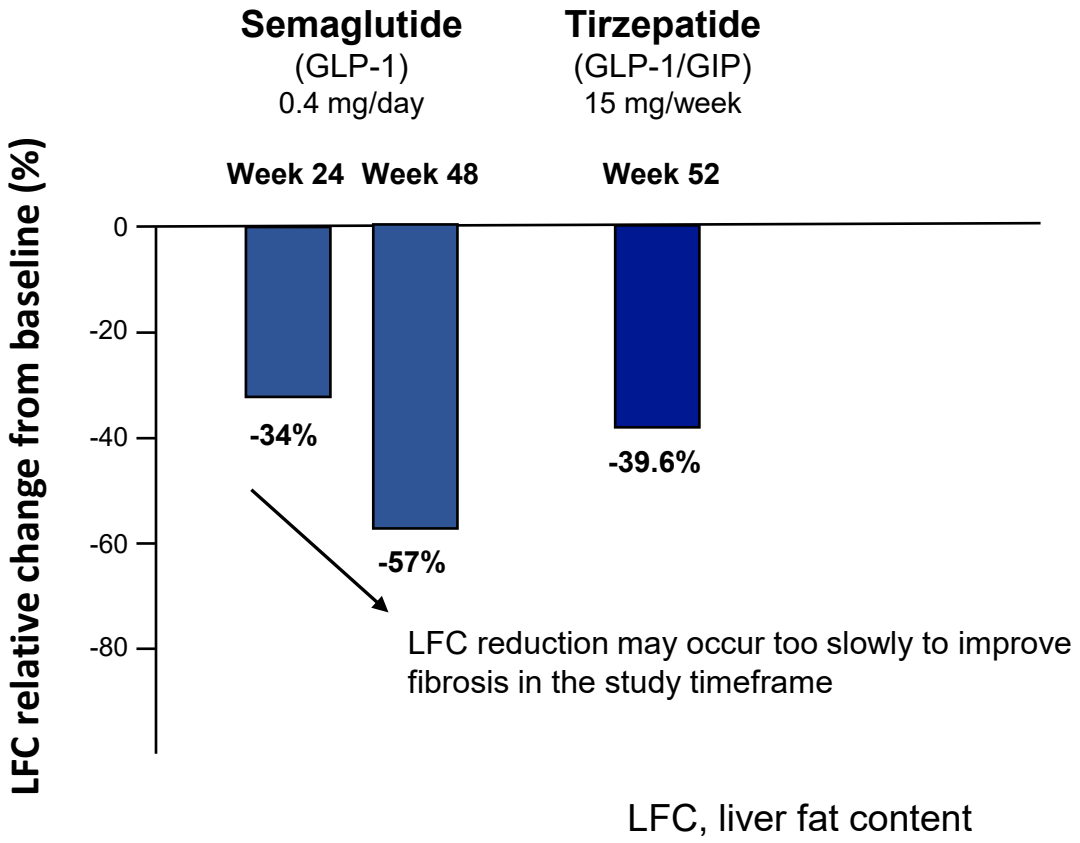
GLP-1 AND GIP AGENTS DISPLAY UNIMPRESSIVE EFFECTS ON LIVER FAT CONTENT

ABSENCE OF GLP-1 AND GIP RECEPTORS IN LIVER



LFC, liver fat content

Flint, Aliment Pharm Ther 2021; Gastadelli, Lancet Diabetes Endocrinol 2022; Harrison, AASLD 2022

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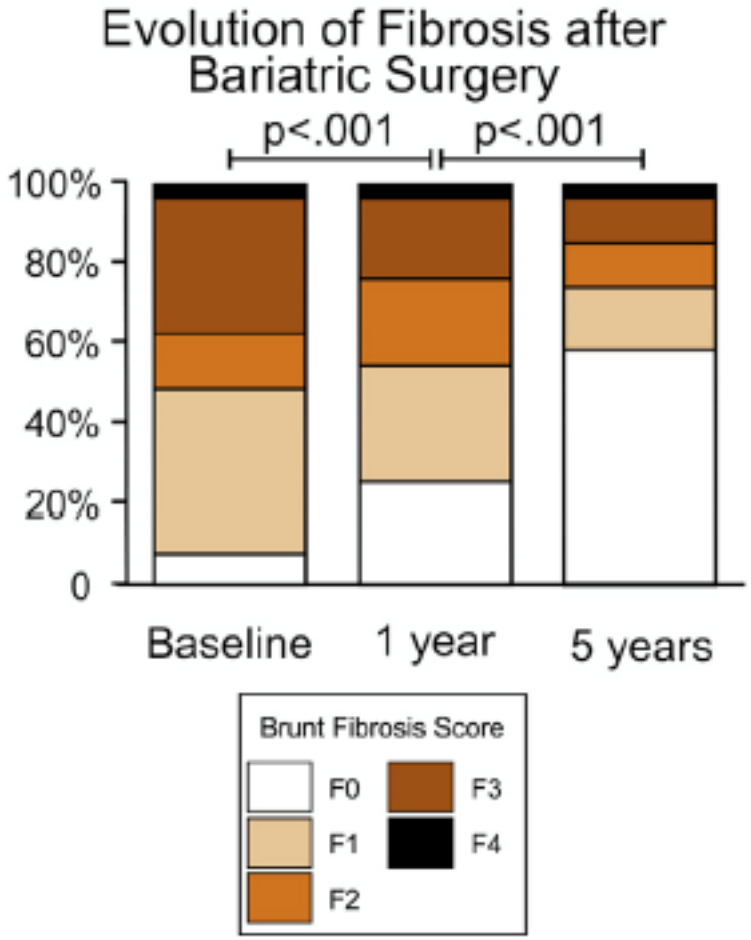
THE IMPACT OF WEIGHT LOSS ON LIVER FIBROSIS MAY BE SLOW

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



Lassailly Gastroenterology 2020

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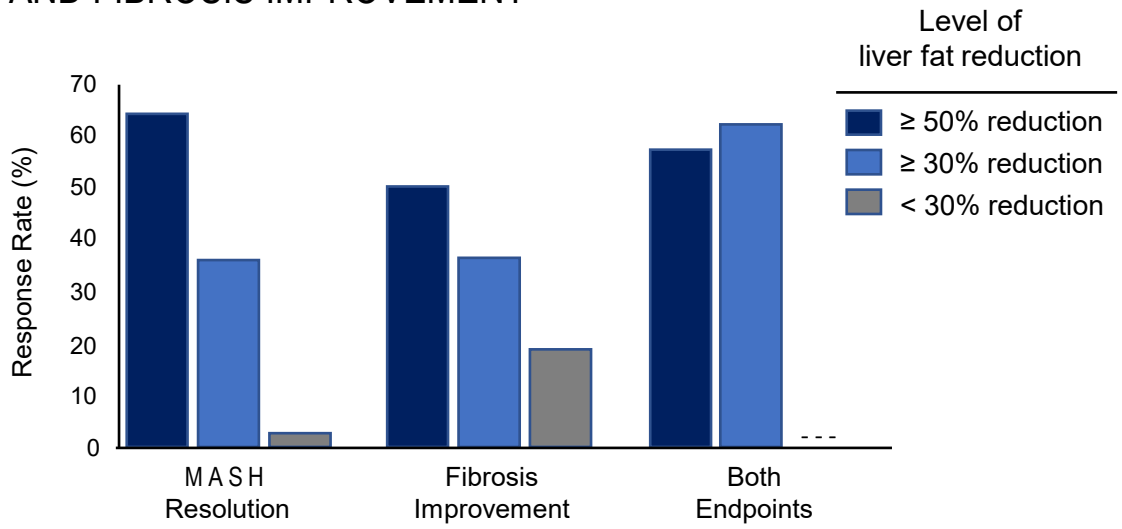
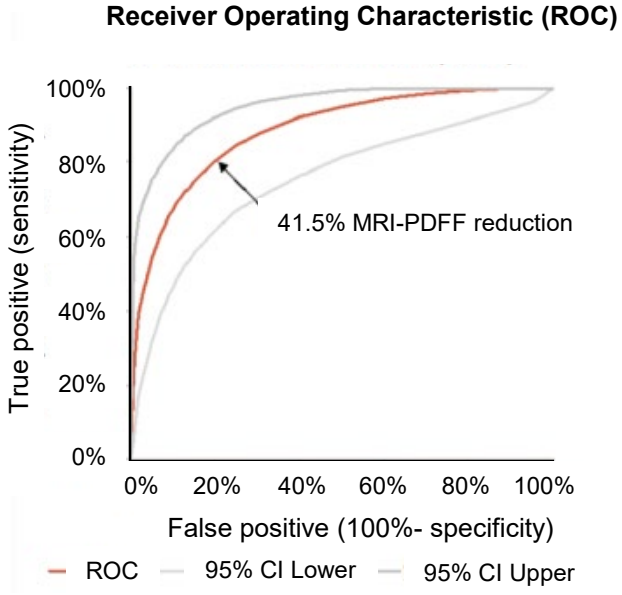
LIVER FAT REDUCTION IMPROVES OUTCOMES ON LIVER BIOPSY

GREATER REDUCTIONS LEAD TO HIGHER RATES OF MASH RESOLUTION AND FIBROSIS IMPROVEMENT

- 30% and 50% reductions in liver fat content were associated with higher rates of MASH resolution and fibrosis improvement
- 41.5% liver fat reduction was identified on ROC analysis as the cutoff for achieving MASH resolution





Adapted from Loomba, European Association for the Study of the Liver, International Liver Conference, 2020, analysis of Phase 2 resmetirom study (Harrison SA, Lancet 2019)

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FIBROSIS IMPROVEMENT DRIVEN BY LIVER FAT REDUCTION

EFFECTS ARE INDEPENDENT OF MECHANISM

Agents with Direct Effects on Liver - 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%
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

Agents with Indirect Effects on Liver - 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

Good established correlation between Liver Fat Reduction and fibrosis improvement…
Pemvidutide clearly demonstrates its promise to be superior

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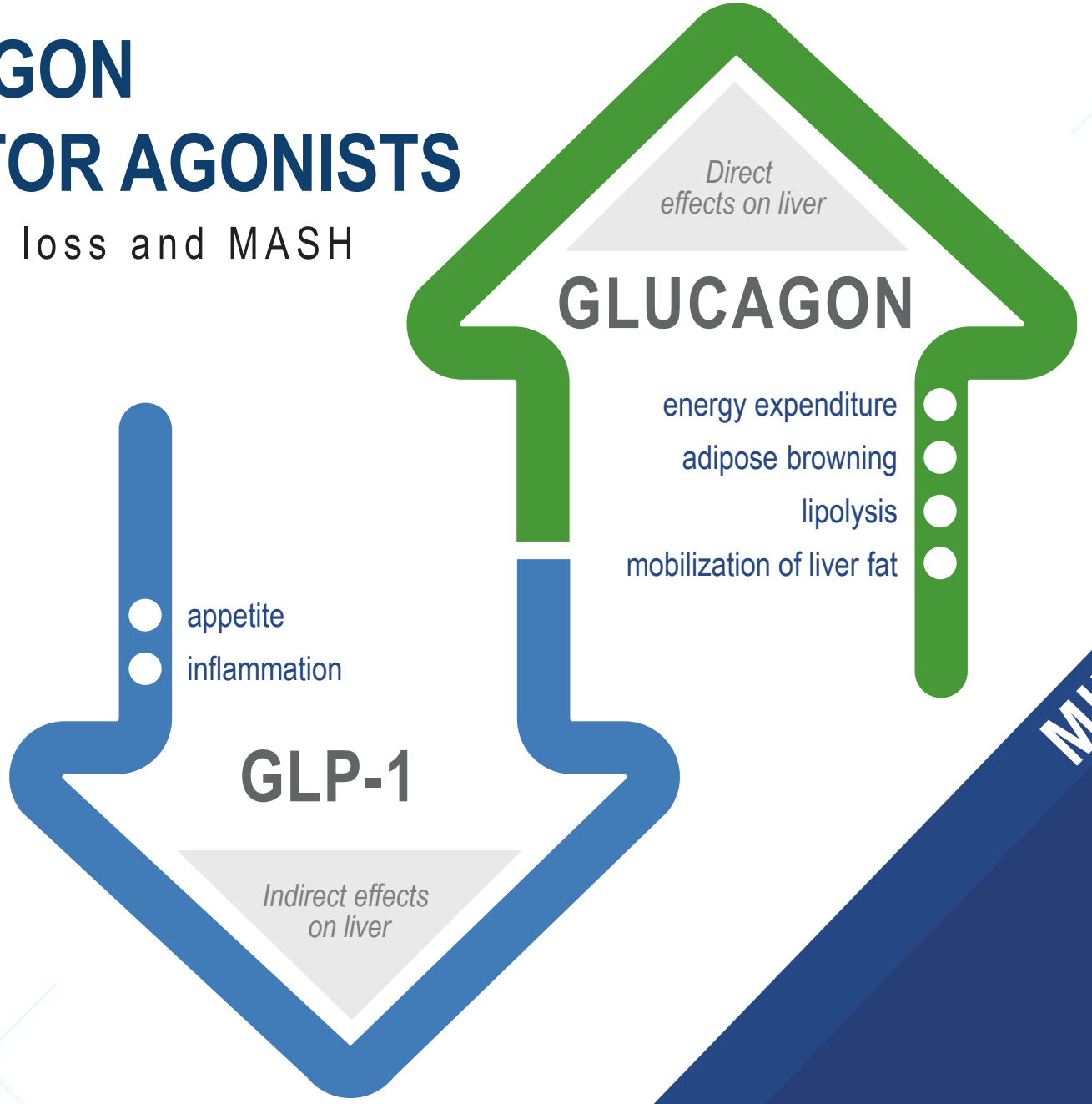
GLP-1/GLUCAGON DUAL RECEPTOR AGONISTS

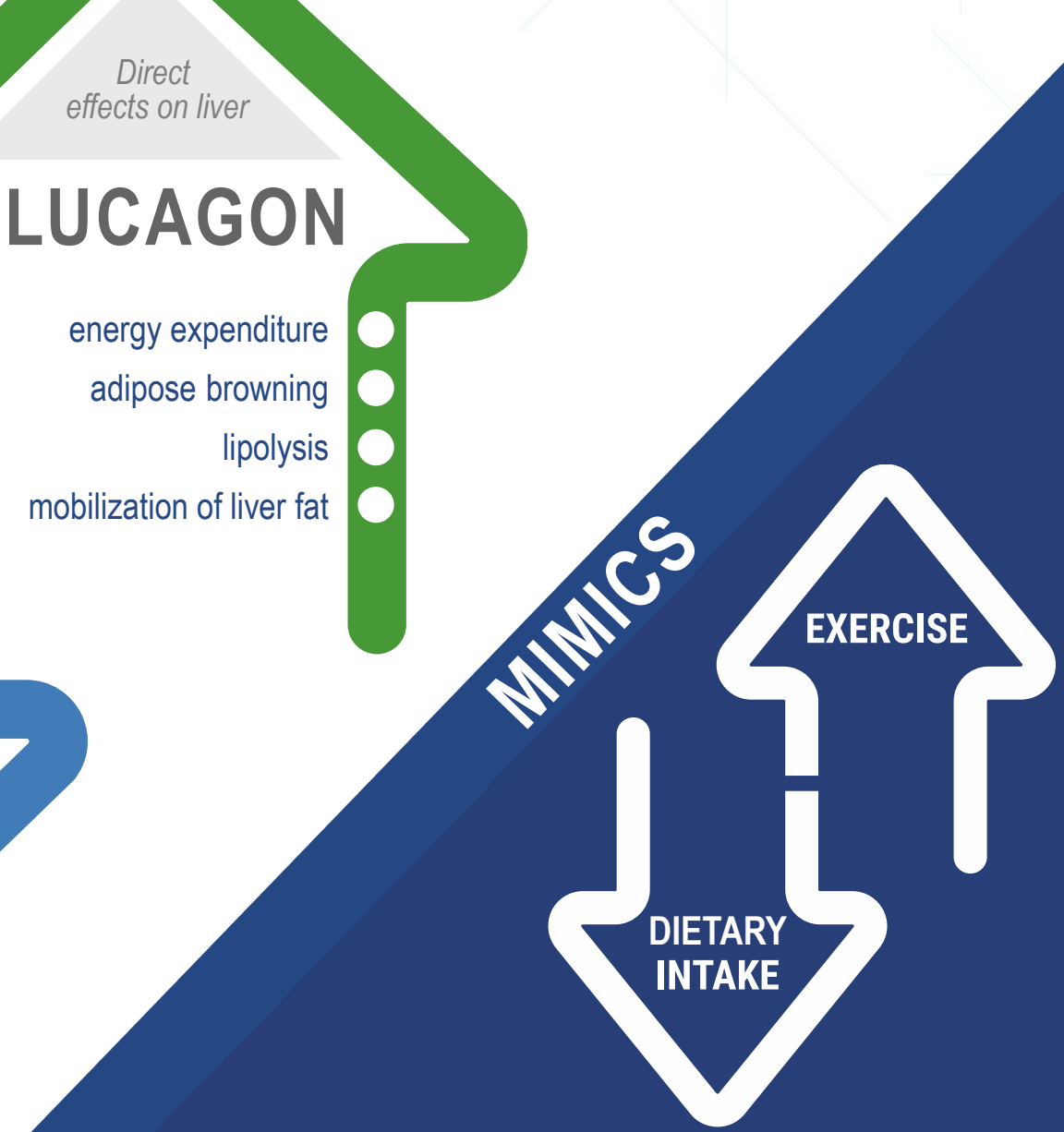
Optimized for weight loss and MASH

Designed for significant reductions in:

BODY WEIGHT

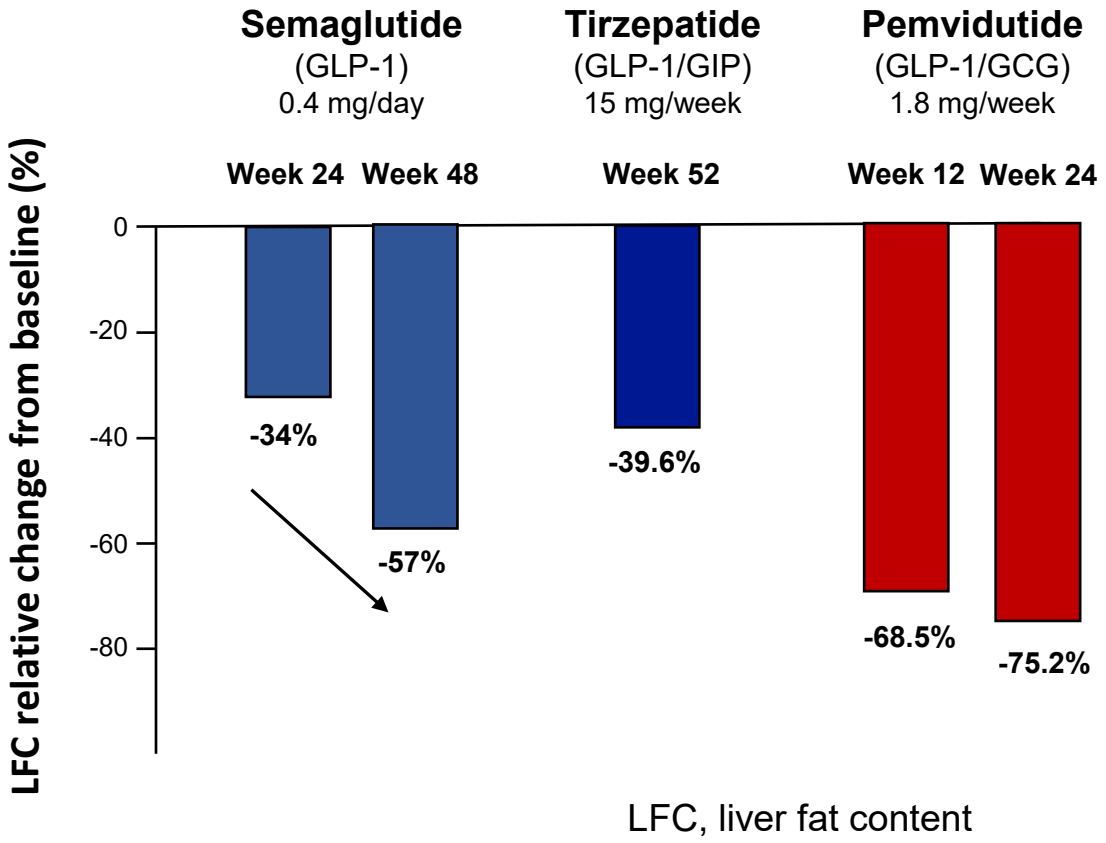
LIVER FAT, INFLAMMATION, & RESULTING FIBROSIS





GLUCAGON AGENTS EXERT RAPID AND POTENT EFFECTS ON LIVER FAT CONTENT

REFLECT THE PRESENCE OF RECEPTORS IN LIVER



LFC, liver fat content

Flint, Aliment Pharm Ther 2021; Gastadelli, Lancet Diabetes Endocrinol 2022; Harrison, AASLD 2022

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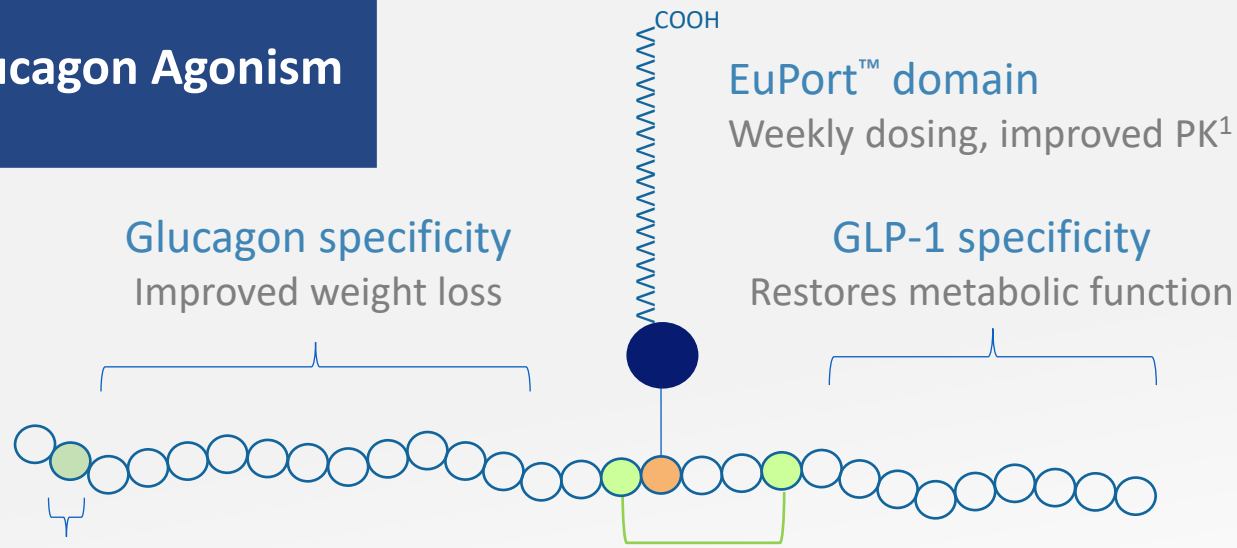
PEMVIDUTIDE

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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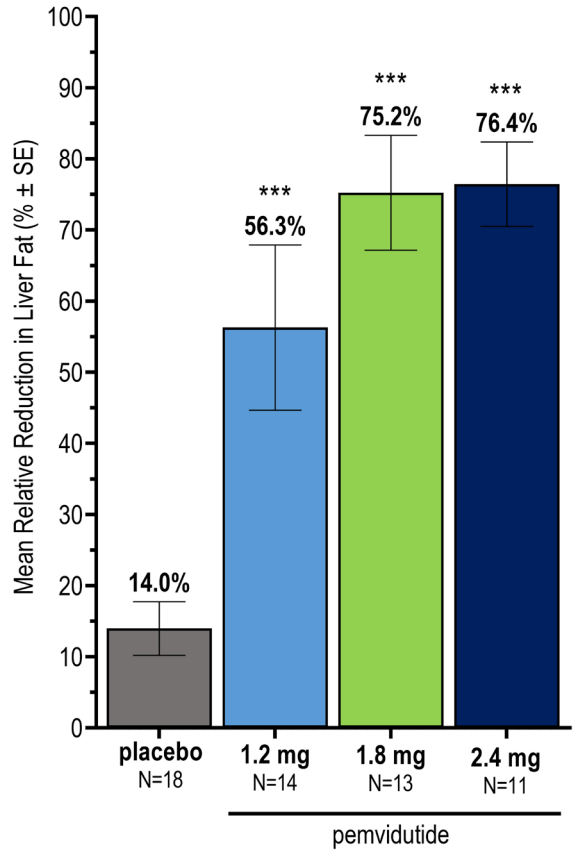
PEMVIDUTIDE— ROBUST REDUCTIONS IN LIVER FAT CONTENT AT 24 WEEKS

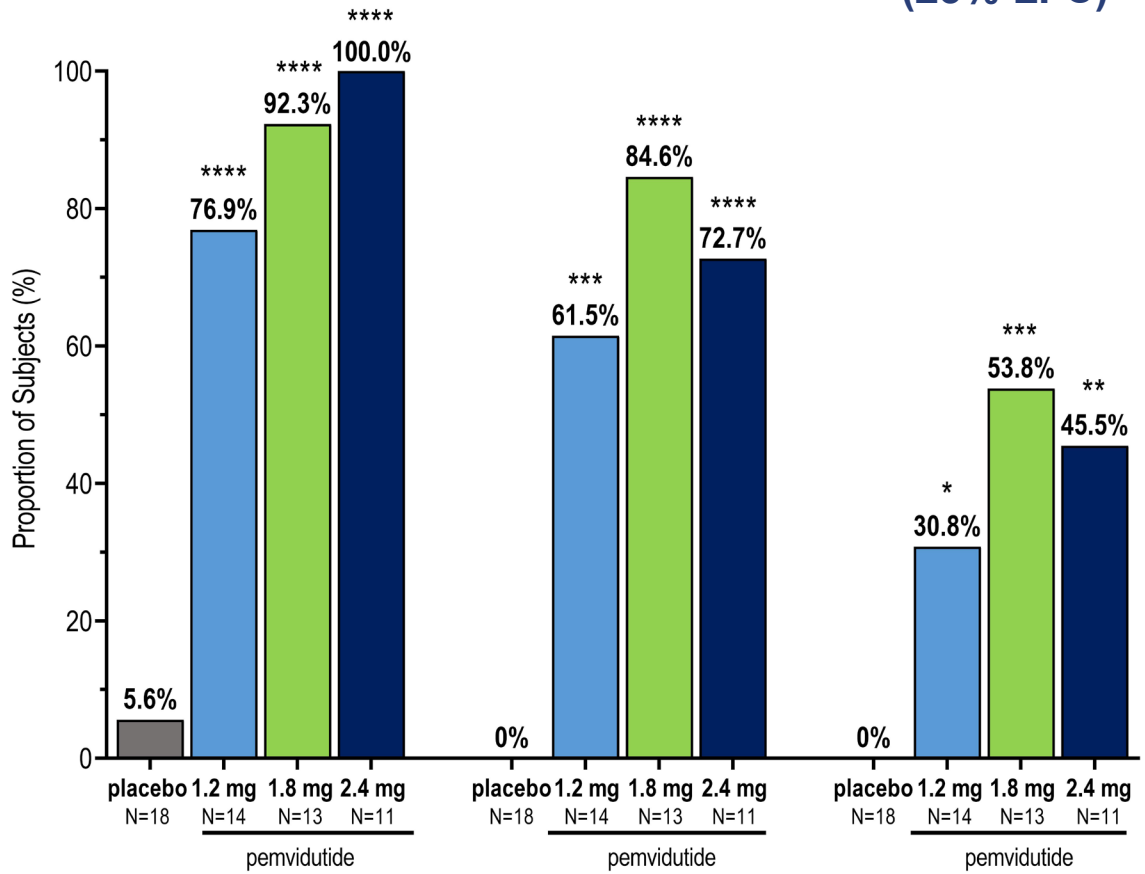
CORRELATES WITH MASH RESOLUTION AND FIBROSIS IMPROVEMENT

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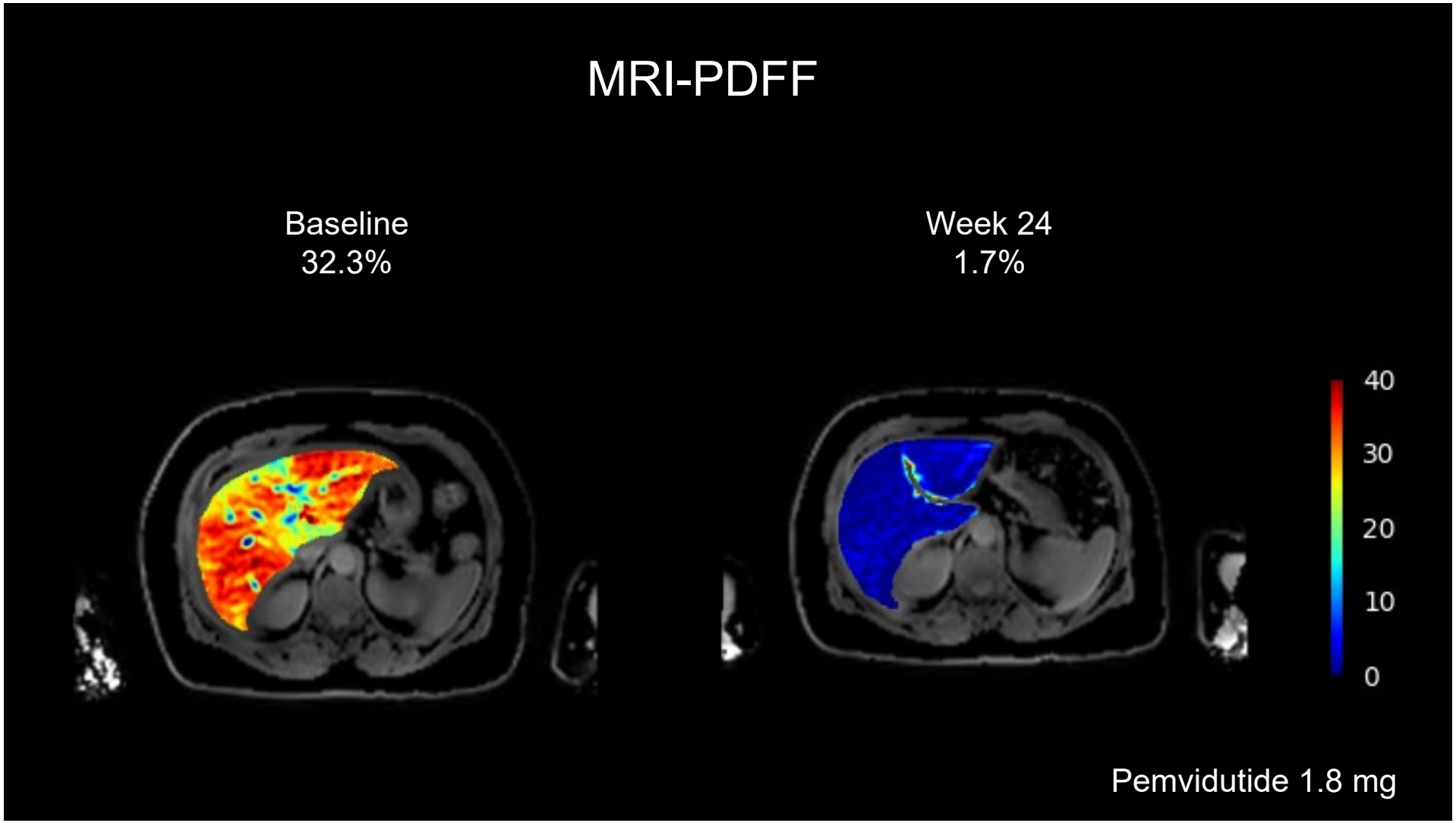
PEMVIDUTIDE— MARKED REDUCTION OF LIVER FAT CONTENT BY MRI-PDFF AT WEEK 24



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

Study ALT-801-106 MASLD Trial

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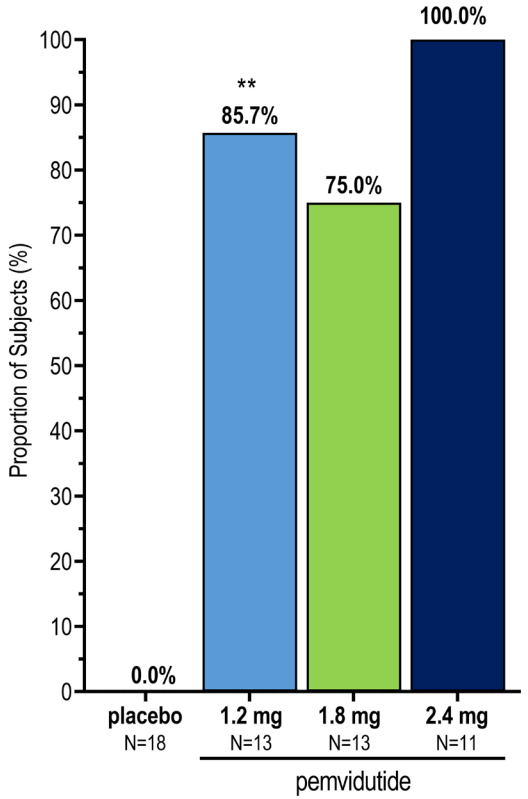
PEMVIDUTIDE— SIGNIFICANT ALT REDUCTIONS AND cT1 RESPONSE RATES

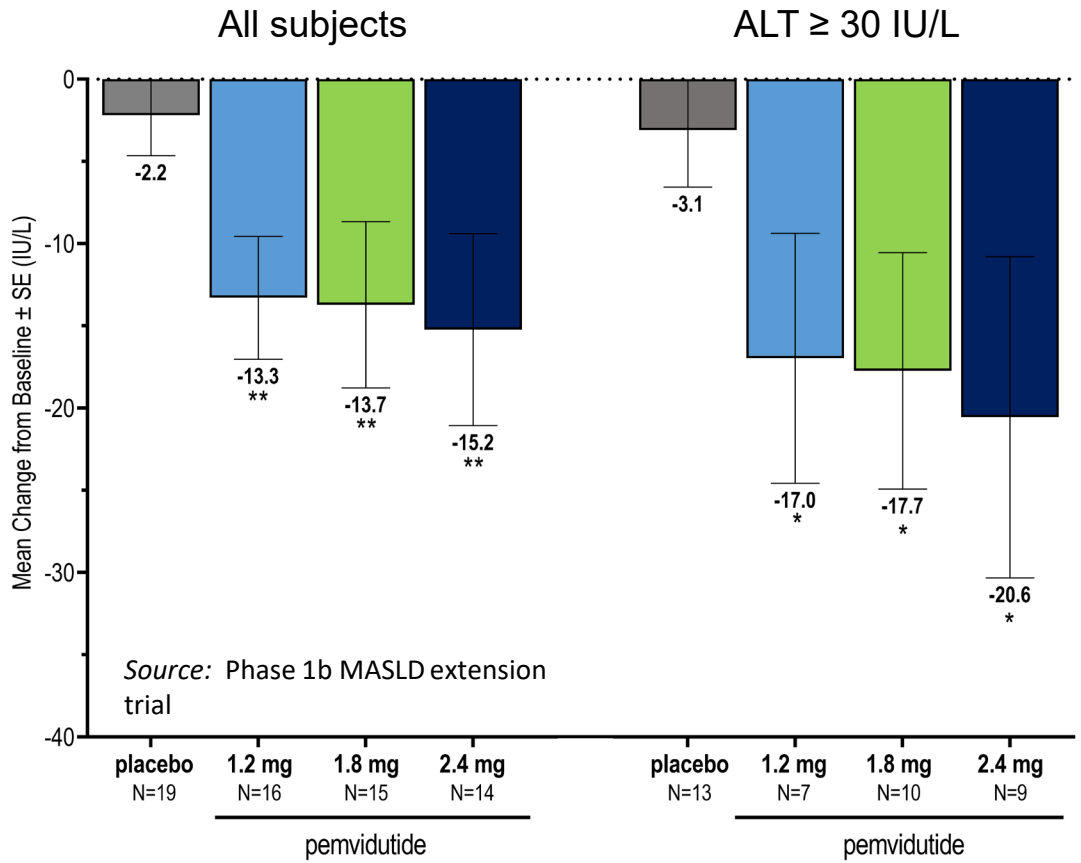
TWO INDEPENDENT INDICATORS OF REDUCED LIVER INFLAMMATION AND NAFLD ACTIVITY SCORE (NAS)

cT1 Responder Rates[1] at Week 24



* p < 0.05, ** p < 0.005 vs. placebo (Fisher's Exact Test)

ALT Reduction at Week 24



* p < 0.05, ** p < 0.005 vs. placebo (MMRM[3])

[1]80ms reduction from baseline; [2]Dennis A, Front Endocrinol 2021; 3 mixed model for repeated measures

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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	+	++++
BI456906	GLP-1/GCG	8:1	yes	—	++++
Cotadutide	GLP-1/GCG	5:1	yes	++	+
Retatrutide	GLP-1/GIP/GCG	1:6:0.1	yes	++++	++++
Efinopegdutide	GLP-1/GCG	2:1	yes	++++	++++
Pemvidutide	GLP-1/GCG	1:1	no	++++	++++

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

THANK YOU