Redefining and Executing Dual Agonist Enterohormone Therapies for Obesity

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Novel Therapies for Type 2 Diabetes and Obesity Summit
31 May 2023

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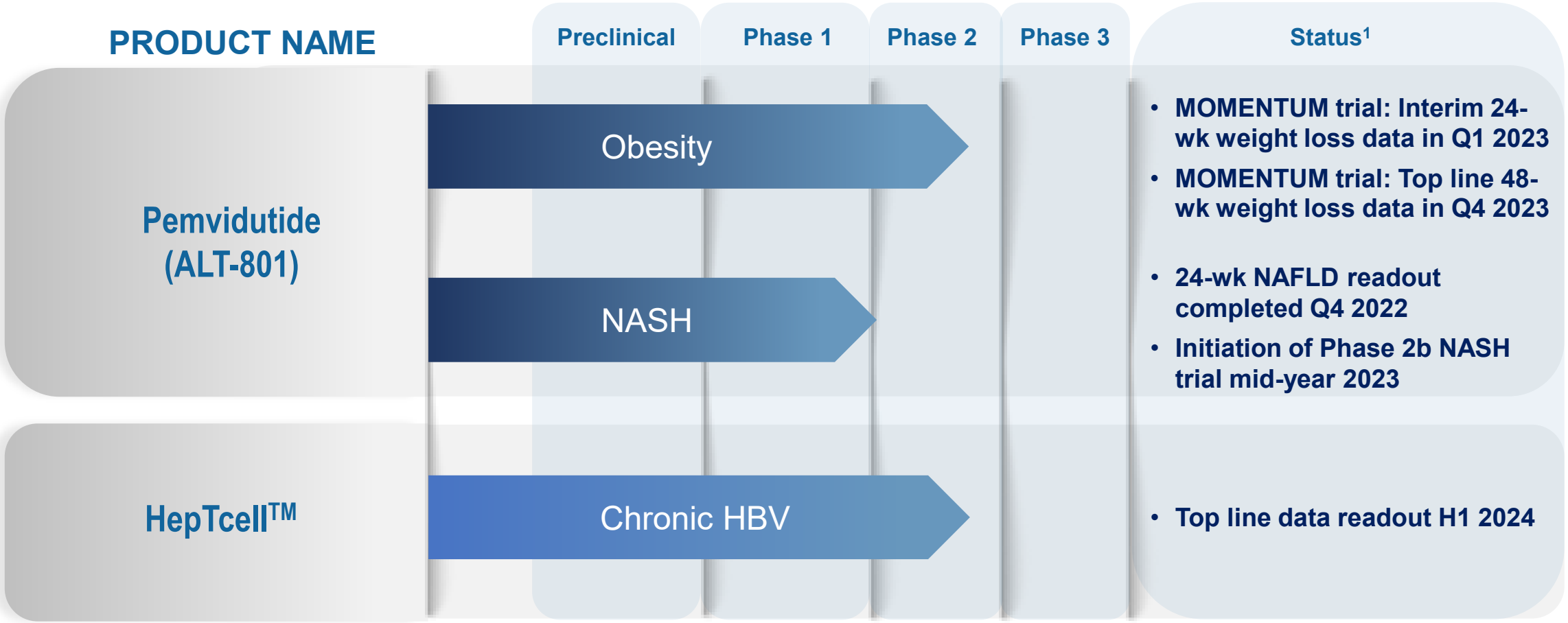
Altimmune—Focused Pipeline

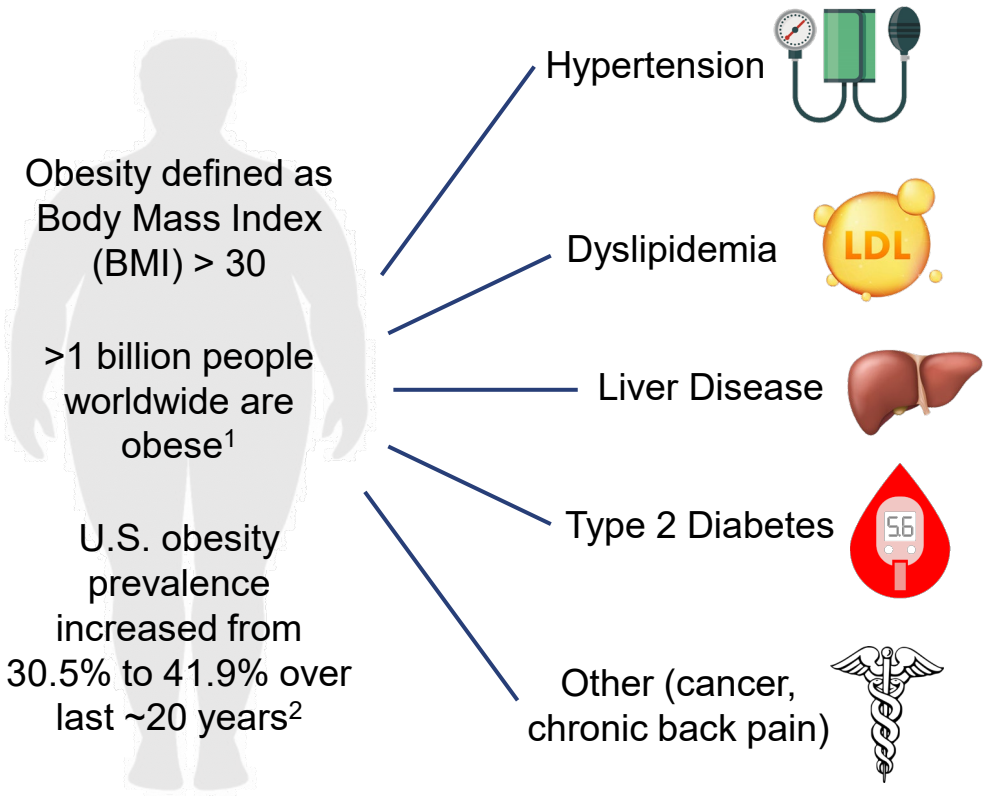
PEPTIDE-BASED THERAPEUTICS TARGETING OBESITY AND LIVER DISEASES



[1] *Expected Dates*

Obesity—Unmet Medical Need and Burden

Significant Unmet Need



Substantial Burden

- **Coronary heart disease, dyslipidemia and hypertension** represent approximately **50% of the deaths** attributable to obesity[2]
- **Economic (direct and indirect) costs** of overweight and obesity in 2019 were estimated to be **$844 billion in the Americas**[3]
- U.S. obesity-related **(direct) medical costs** for adults were estimated to be nearly **$173 billion**[4]
- U.S. medical costs for people with obesity tend to be **30% to 40% higher** than those for people without obesity[5]
- Obesity accounts for **47.1% of the total cost of chronic diseases nationwide**[6]

1) World Health Organization. (2022, March 4). *World Obesity Day 2022—Accelerating action to stop obesity.* https://www.who.int/news/item/04-03-2022-world-obesity-day-2022-accelerating-action-to-stop-obesity
2) Lopez, Claude, et.al. (2020) *Weighing Down America: 2020 Update.* Milken Institute. https://milkeninstitute.org/report/weighing-down-america-2020-update
3) Okunogbe A, Nugent R, Spencer G, et al. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Global Health* 2022;7:e009773.
4) Ward ZJ, Bleich SN, Long MW, Gortmaker SL. (2021) Association of body mass index with health care expenditures in the United States by age and sex. PLoS ONE 16(3): e0247307. https://doi.org/10.1371/journal.pone.0247307
5) Tiwari A, Balasundaram P. Public Health Considerations Regarding Obesity. [Updated 2022 Sep 3]. In: StatPearls https://www.ncbi.nlm.nih.gov/books/NBK572122/
6) Waters, H., et. al. (2018, October). Americas Obesity Crisis – The Health and Economic Costs of Excess Weight. Milken Institute. https://milkeninstitute.org/report/americas-obesity-crisis-health-and-economic-costs-excess-weight

US Prevalence and Significance of Obesity Comorbidities

* U.S. prevalence numbers based on 112 million obesity population and each comorbidity percents

Most prevalent comorbidities are dyslipidemia, NAFLD, and hypertension

1) Bays, Harold, et. al. (2013) Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association. Journal of Clinical Lipidology 7(4):304–383.
2) Pantalone KM, et al. Prevalence and recognition of obesity and its associated comorbidities. BMJ Open 2017;7:e017583. doi:10.1136/ bmjopen-2017-017583
3) Romero-Corral, Abel, et. al. (2010) Interactions Between Obesity and Obstructive Sleep Apnea. Chest 137(3): 711-719.
4) Garvey JF, Pengo MF, Drakatos P, Kent BD. Epidemiological aspects of obstructive sleep apnea. J Thorac Dis 2015;7(5):920-929.
5) Lim Y, Boster J. Obesity and Comorbid Conditions. [Updated 2023 Feb 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; https://www.ncbi.nlm.nih.gov/books/NBK574535/
6) Quek, Jingxuan, et. al. (2023) Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population:. The Lancet Gastroenterology & Hepatology 8(1):20-30.
7) Vernon, G, et. al. (2011) Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 34:274–285.
8) Le, Michael, et. al. (2022) 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology 2022;20:2809–2817
9) Dufour, Jean-François, et. al. (2021) The global epidemiology of nonalcoholic steatohepatitis (NASH) and associated risk factors–A targeted literature review. Endocrine and Metabolic Science 3.

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

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%††
Efruxifermin (70 mg)	Harrison SA 2022[5]	FGF21 agonist	2.6%
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

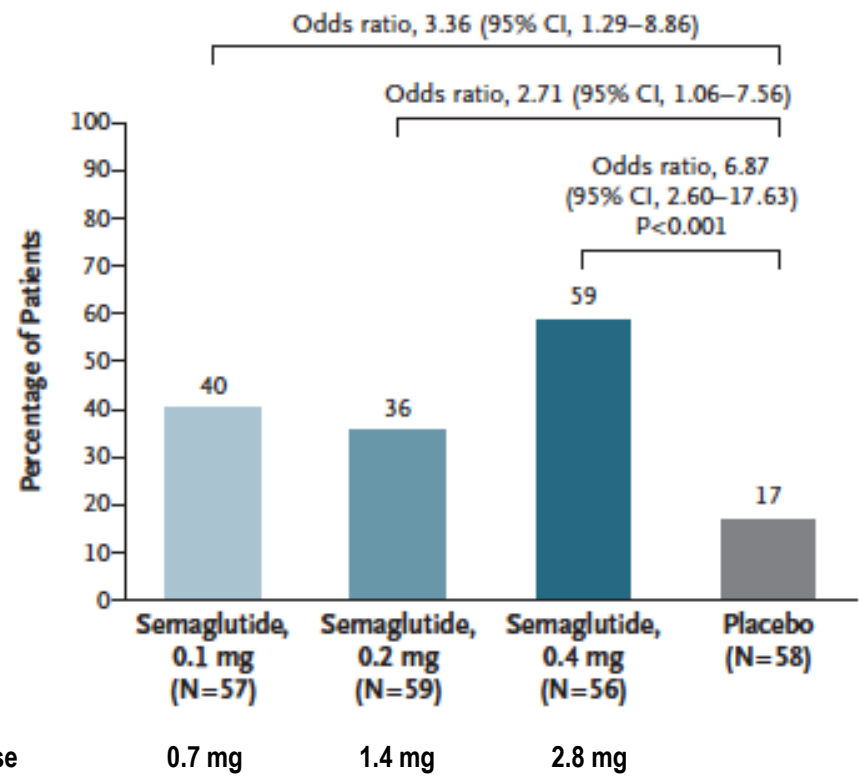
†† Weight loss of 3.9% reported in ENLIVEN Trial press release (April 2023)

[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] Harrison SA et al (2022) , AASLD, The Liver Meeting 2022; [6] Lawitz, EJ, et al. (2018) Clin Gastroenterol Hepatol 16:1983-91; [7]Franque S, AASLD 2020

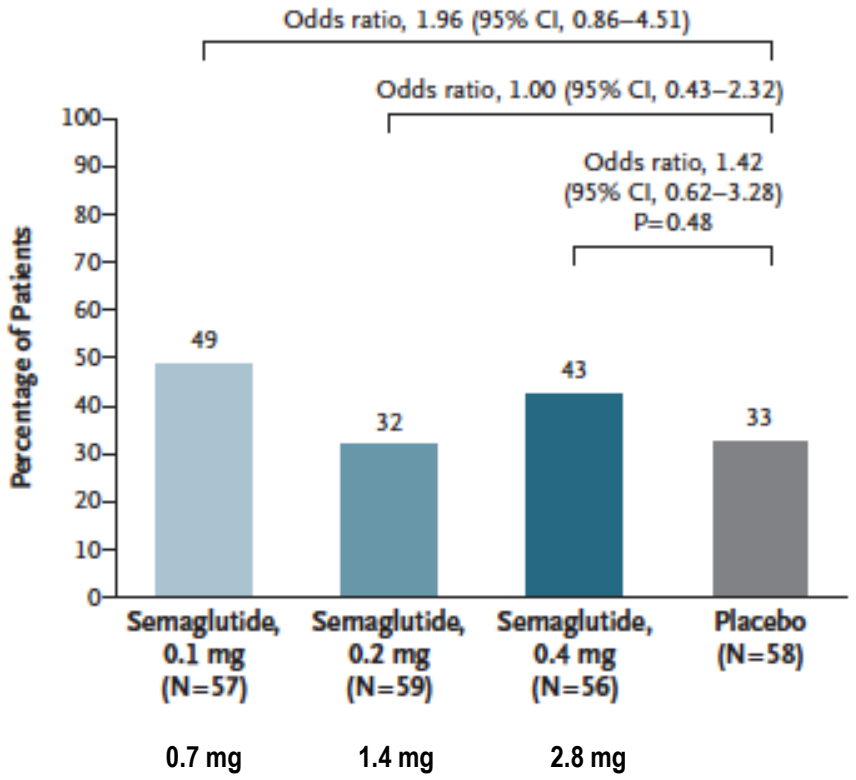
Semaglutide—NASH Resolution Without Fibrosis Improvement

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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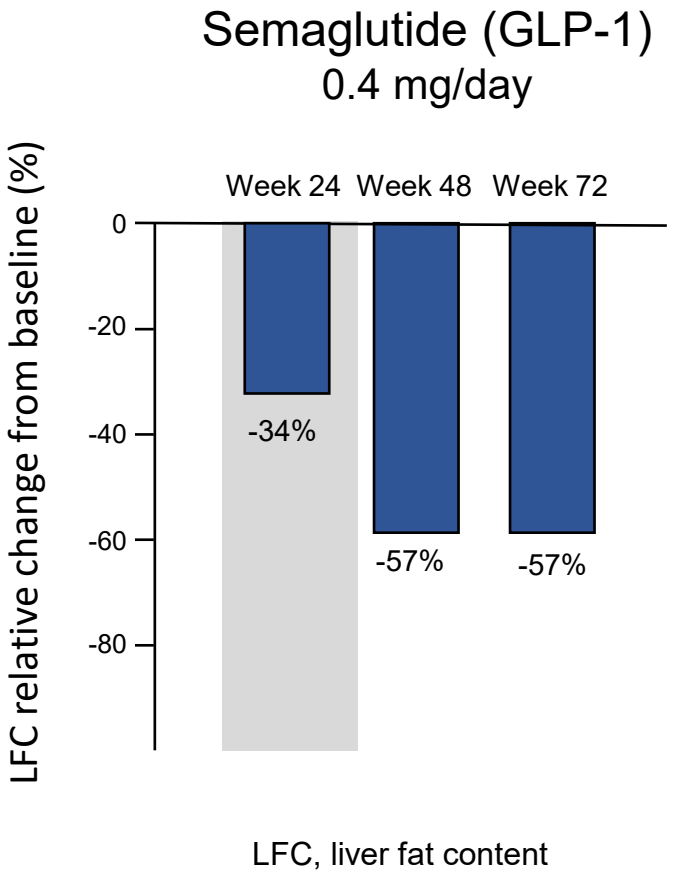
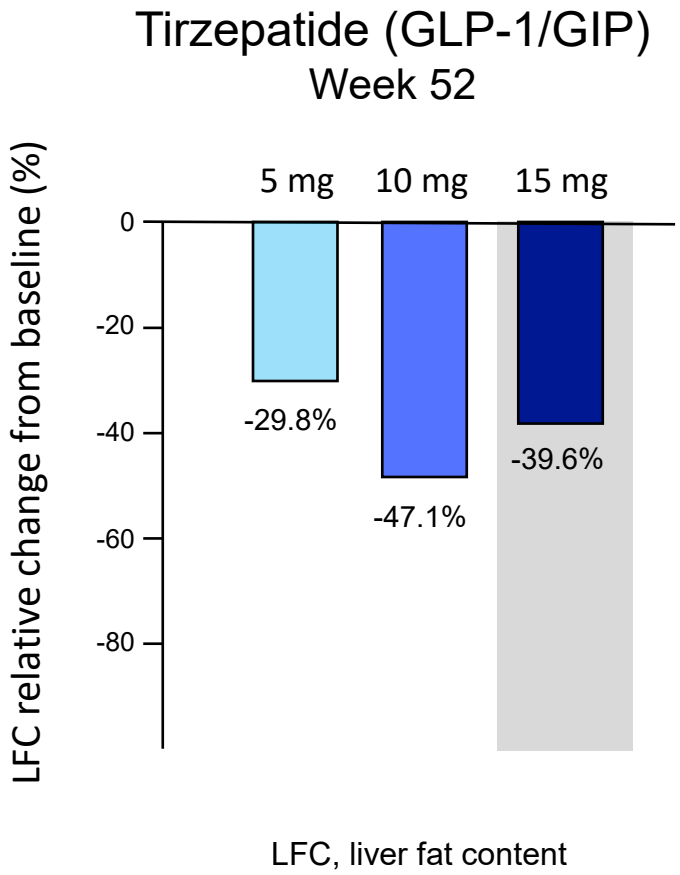
Effects of Semaglutide and Tirzepatide on Liver Fat Content

ABSENCE OF GLP-1/GIP RECEPTOR IN LIVER / LOW OR DELAYED IMPACT WITH WEIGHT LOSS ALONE





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

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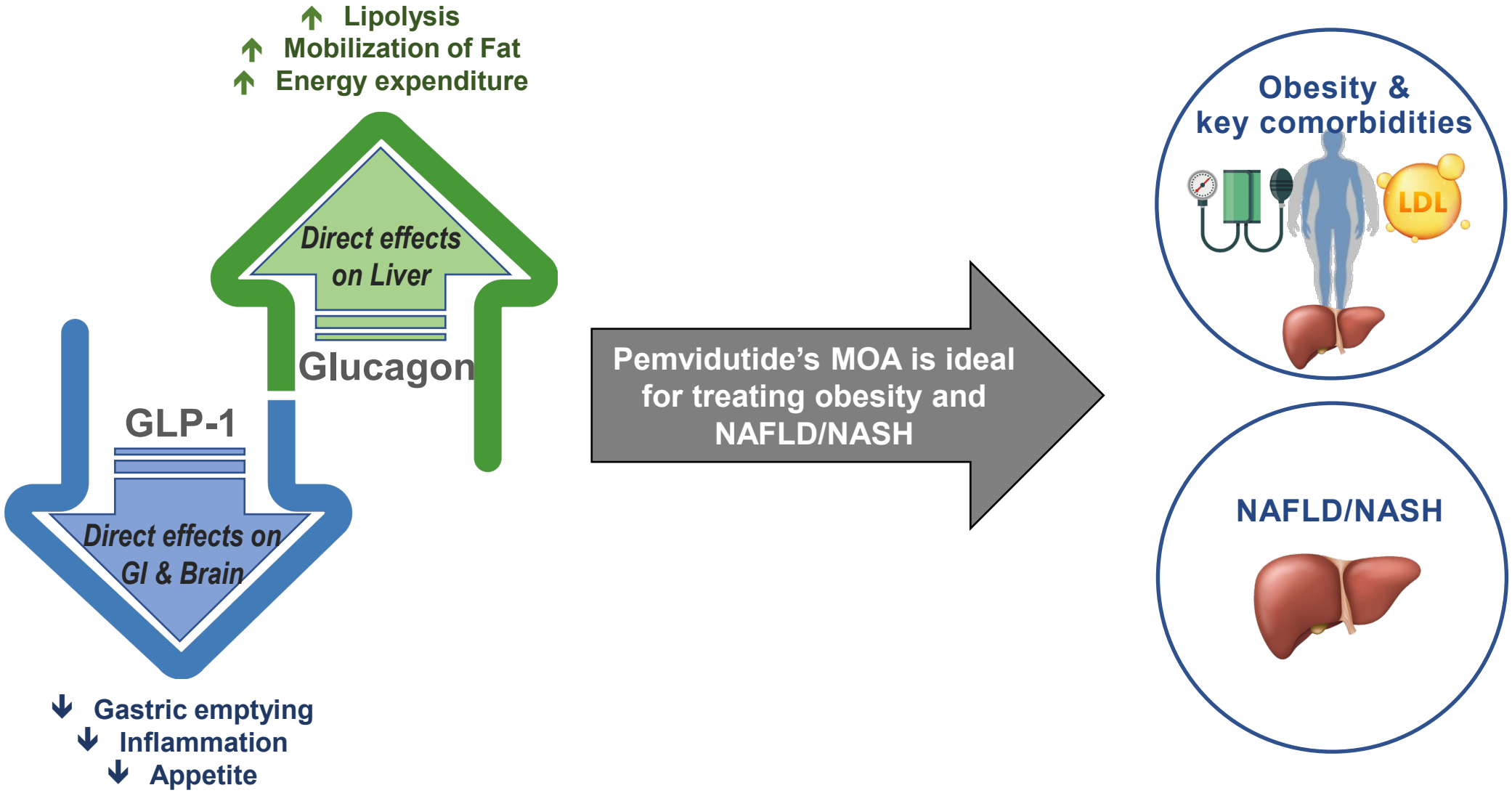
Pemvidutide: GLP-1/Glucagon Dual Receptor Agonist

OPTIMIZED FOR WEIGHT LOSS, NASH, AND COMORBIDITIES



Pemvidutide is a Balanced GLP-1/Glucagon Dual Agonist

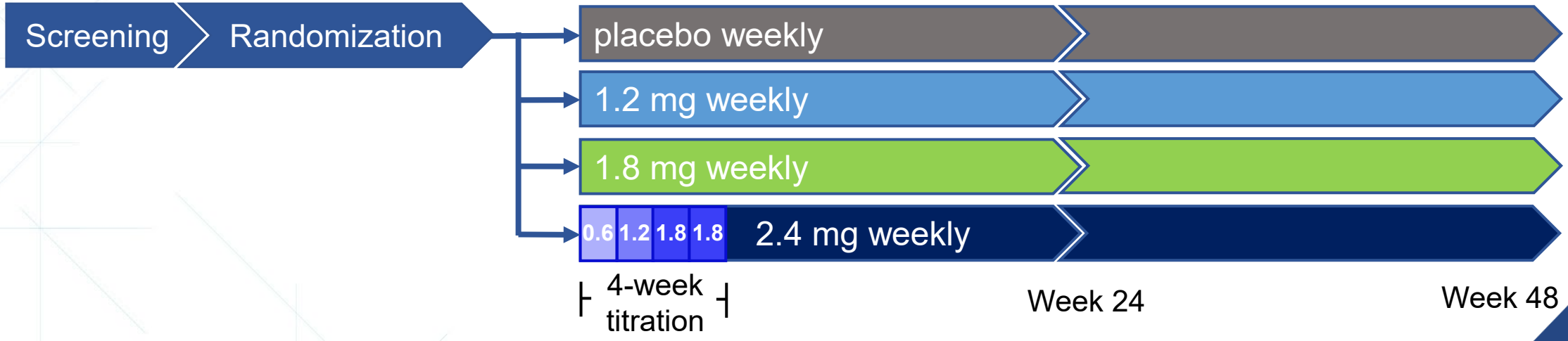
Semaglutide	Yes	NA	
Tirzepatide	Yes	NA	
AMG-133	Yes	NA	
CagriSema	Yes	NA	GLP / Glucagon
Cotadutide	Yes	Yes	**5**:1[1]
BI-456906	Yes	Yes	**8**:1[2]
Retatrutide	Yes	Yes	**6** (GIP):**1**: 0.1[3]
Pemvidutide	**Yes**	**Yes**	**1:1**[4]

Other programs rely heavily on GLP-1 with modest/little glucagon activity

1) Hope DCD, Vincent ML and Tan TMM (2021) Striking the Balance: GLP-1/Glucagon Co-Agonism as a Treatment Strategy for Obesity. Front. Endocrinol. 12:735019. doi: 10.3389/fendo.2021.735019
2) T. Zimmermann, L. Thomas, T. Baader-Pagler, P. Haebel, E. Simon, W. Reindl, et al. BI 456906: discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy. Mol. Metab., 7 (2022), Article 101633, 10.1016/j.molmet.2022.101633
3) GIP/GLP1/GCG. Coskun, T. et. al. (2021, June 25-29). *The novel GIP, GLP-1, and Glucagon Triple Receptor Agonist LY3437943 Exhibits Robust Efficacy in Preclinical Models of Obesity and Diabetes.* American Diabetes Association –81stAnnual Scientific Sessions.
4) Nestor, J. J., Zhang, X., Jaw-Tsai, S., Parkes, D. G. & Becker, C. K. Design and characterization of a surfactant-conjugated, long-acting, balanced GLP-1/glucagon receptor dual agonist. Pept. Sci. https://doi.org/10.1002/pep2.24221 (2021).

MOMENTUM Obesity Trial Design

- Phase 2, 48-week trial of pemvidutide in ~ 320 subjects with overweight or obesity
- Randomized 1:1:1:1 to 4 treatment arms, stratified by sex and baseline BMI, with standard lifestyle interventions
- Rapid (4 week) dose titration for 2.4 mg arm; dose reduction due to intolerability was not allowed
- A pre-specified 24-week interim analysis was performed on 160 subjects



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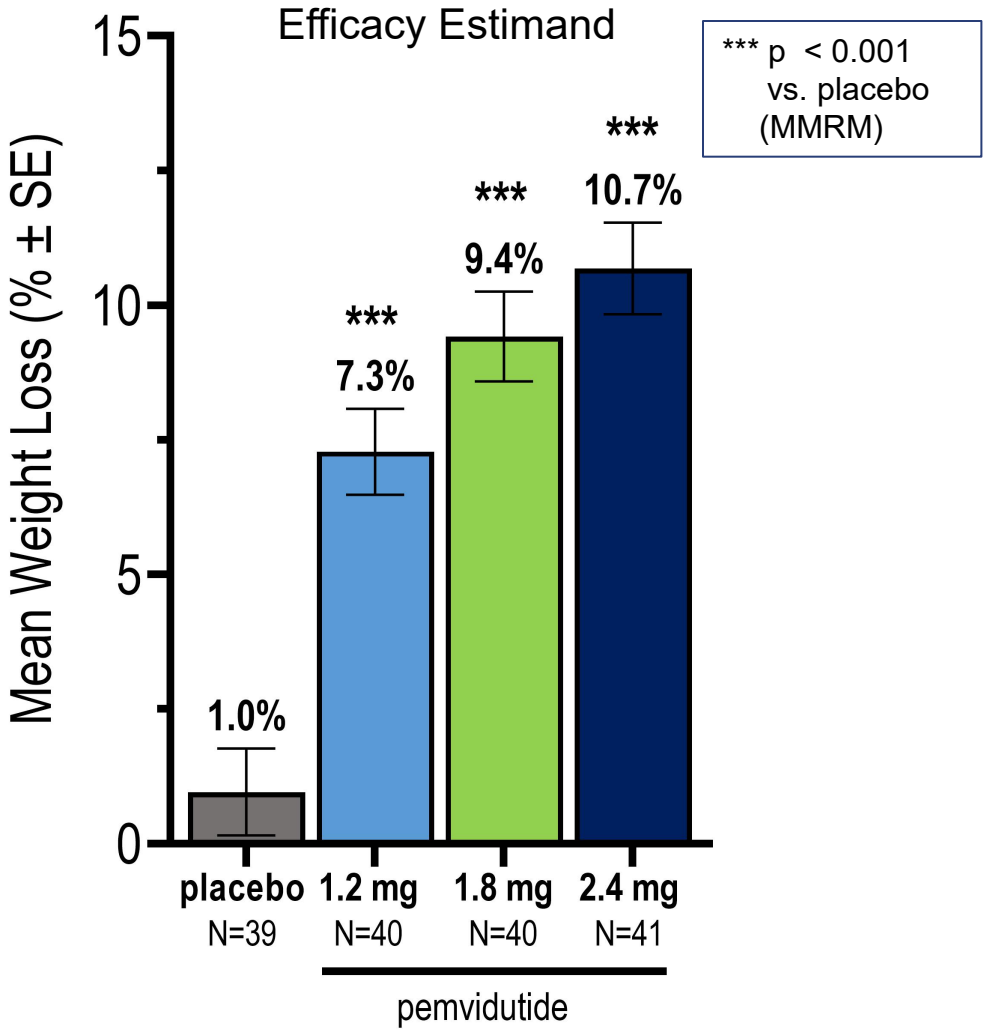
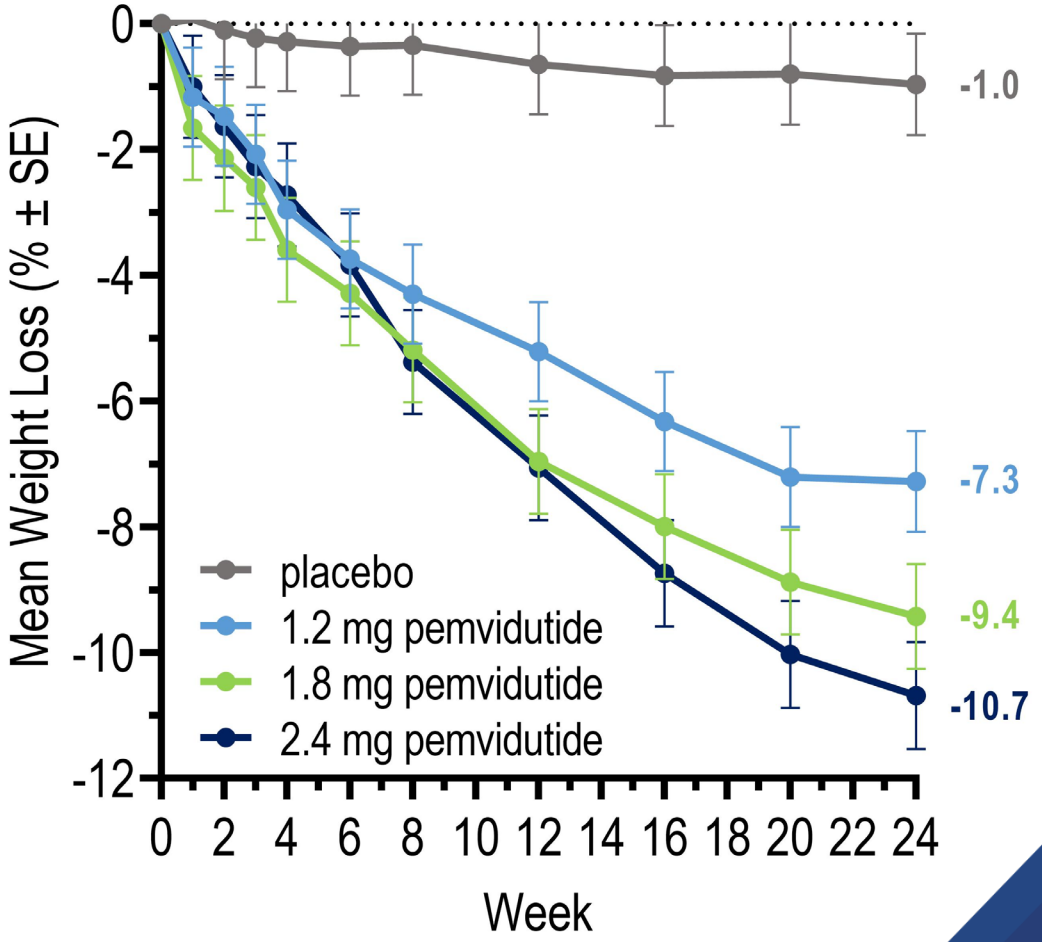
Pemvidutide—Substantial Weight Loss Through Week 24

INTERIM DATA DEMONSTRATES PROMISING WEIGHT LOSS TRENDS





Study ALT-801-211 MOMENTUM Obesity Trial, MMRM, mixed model for repeated measures

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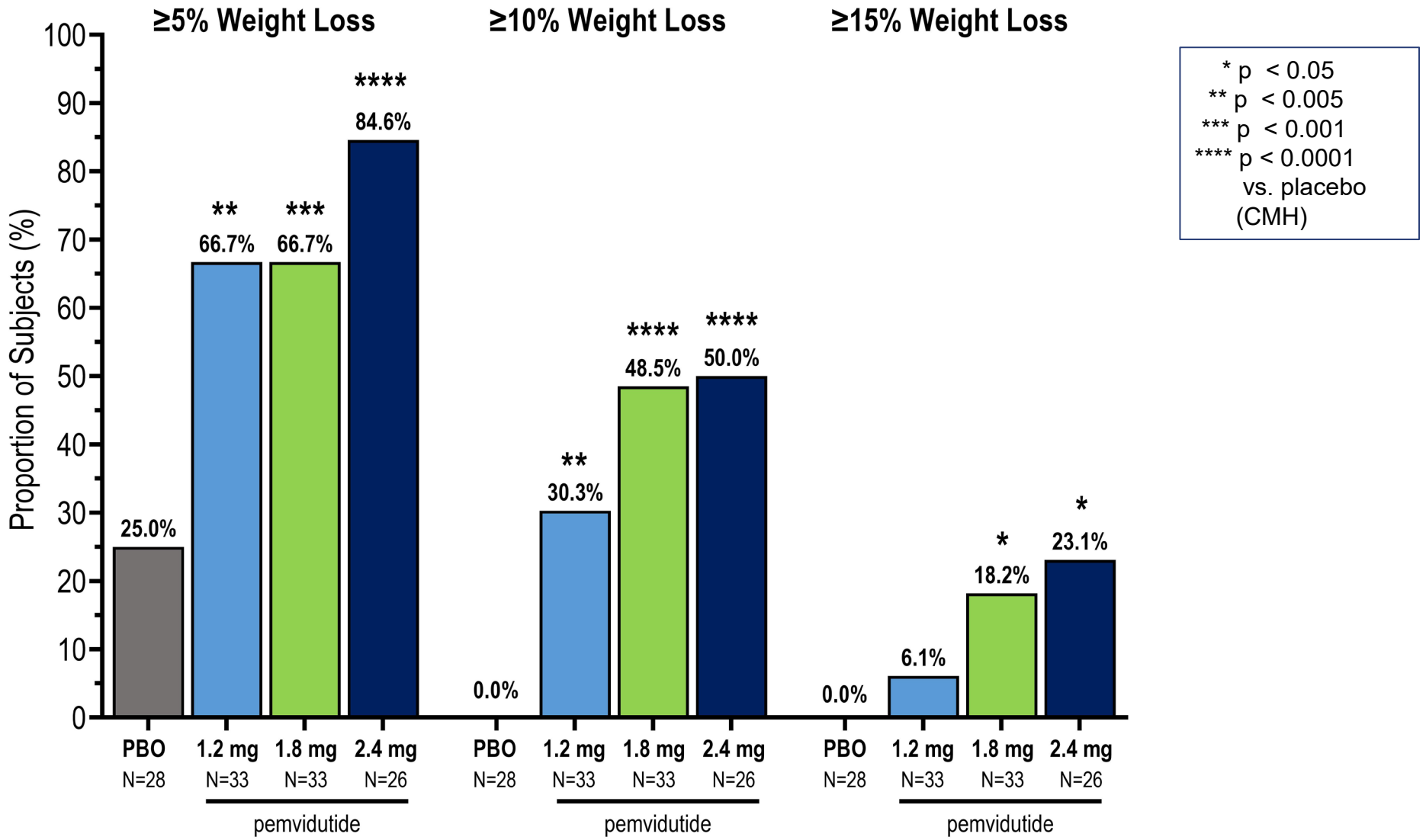
Pemvidutide— Weight Loss Responder Analysis at Week 24

50% OF SUBJECTS LOST 10% BODY WEIGHT AT 24 WEEKS



* p < 0.05
** p < 0.005
*** p < 0.001
**** p < 0.0001
vs. placebo
(CMH)

Study ALT-801-211 MOMENTUM Obesity Trial, CMH, Cochran–Mantel–Haenszel

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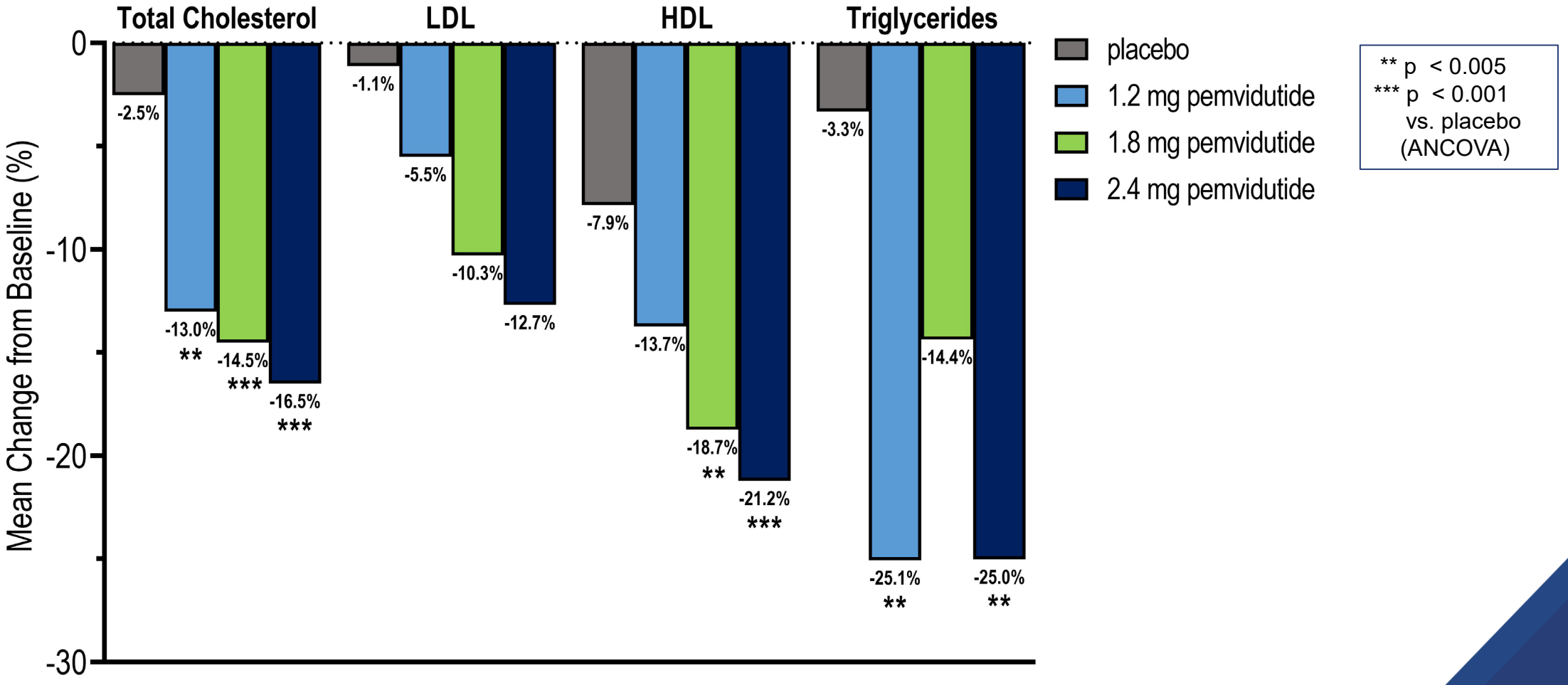
Pemvidutide— Robust Reduction in Serum Lipids at Week 24



Study ALT-801-211 MOMENTUM Obesity Trial, ANCOVA, analysis of covariance

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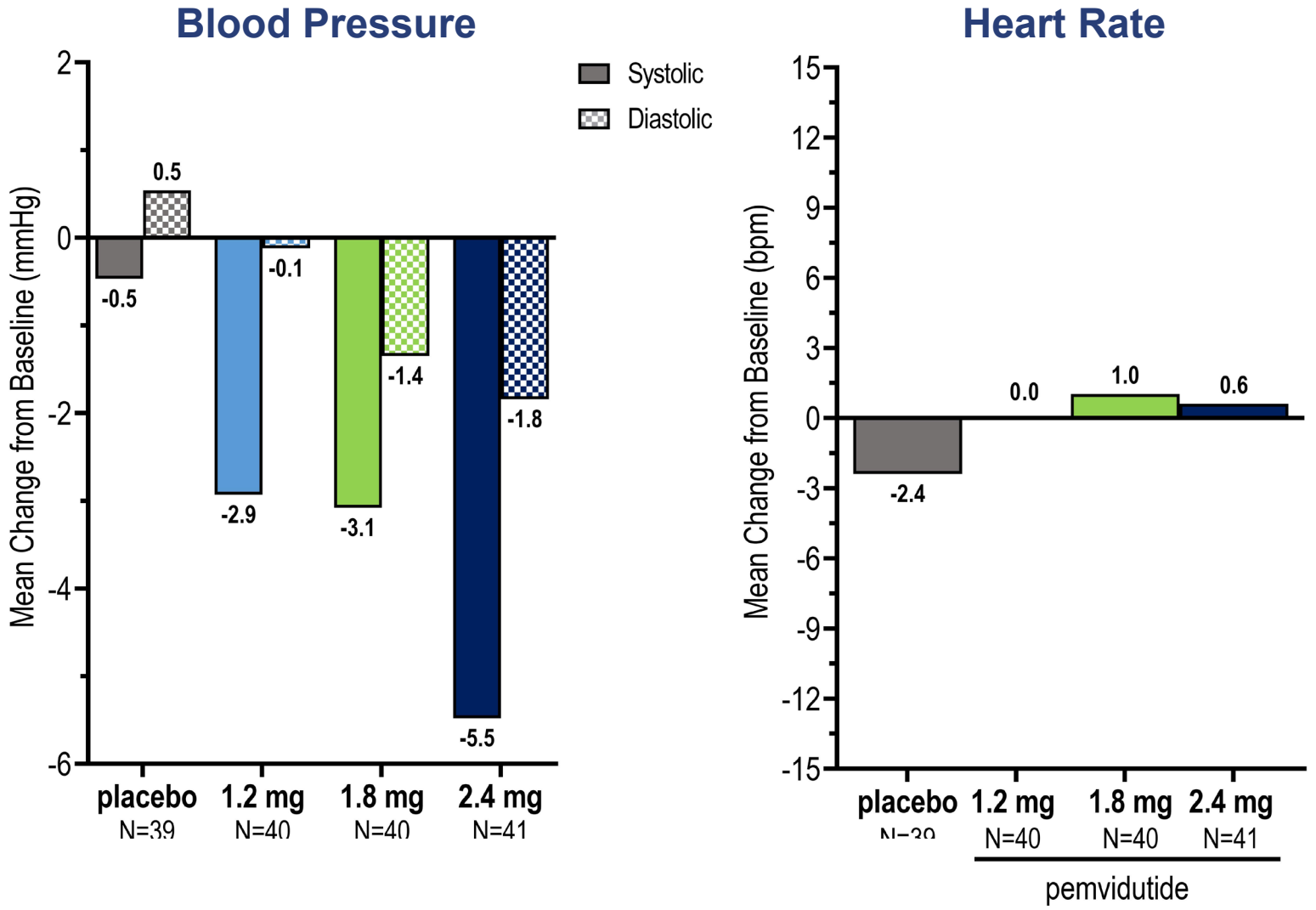
Pemvidutide— Improvements in Blood Pressure without Meaningful Changes in Heart Rate Through Week 24



Study ALT-801-211 MOMENTUM Obesity Trial , MMRM, mixed model for repeated measures

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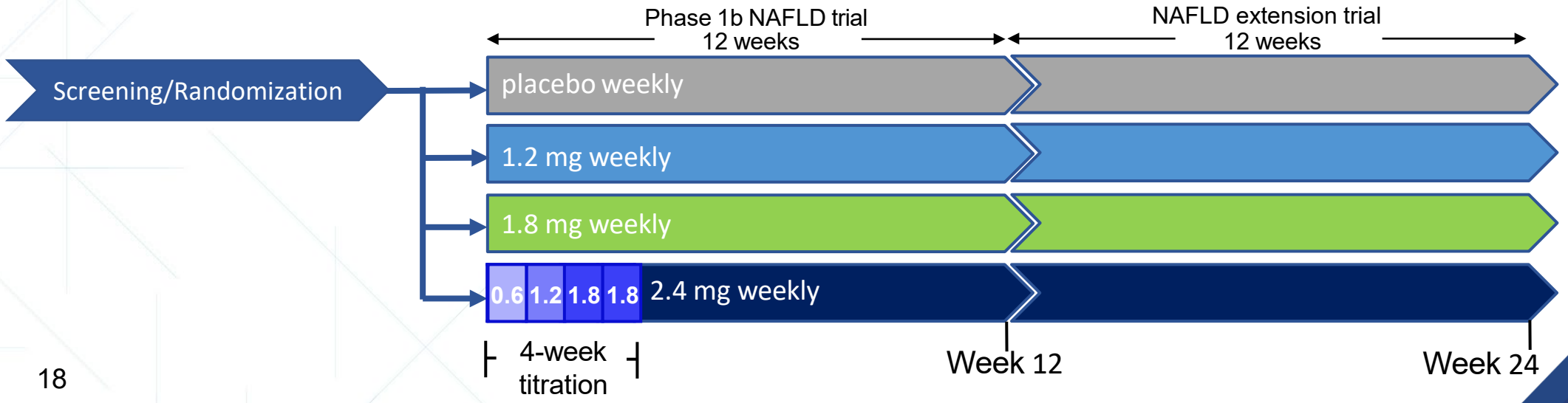
Pemvidutide Safety Overview—Adverse Events (AEs) Through Week 24

Characteristic		Treatment			
		Placebo (n = 39)	1.2 mg (n=40)	1.8 mg (n=40)	2.4 mg (n=41)
Serious adverse events	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)[1]
AEs leading to treatment discontinuation	n (%)	1 (2.6%)	3 (7.5%)	4 (10.0%)	11 (26.8%)
Gastrointestinal AEs					
Nausea					
Mild	n (%)	2 (5.1%)	5 (12.5%)	9 (22.5%)	12 (29.3%)
Moderate	n (%)	0 (0.0%)	3 (7.5%)	13 (32.5%)	9 (22.0%)
Severe	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)
Vomiting					
Mild	n (%)	0 (0.0%)	0 (0.0%)	2 (5.0%)	5 (12.2%)
Moderate	n (%)	0 (0.0%)	2 (5.0%)	3 (7.5%)	4 (9.8%)
Severe	n (%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.4%)
Diarrhea					
Mild	n (%)	0 (0.0%)	3 (7.5%)	2 (5.0%)	4 (9.8%)
Moderate	n (%)	2 (5.1%)	0 (0.0%)	0 (0.0%)	2 (4.9%)
Constipation					
Mild	n (%)	0 (0.0%)	3 (7.5%)	1 (2.5%)	5 (12.2%)
Moderate	n (%)	2 (5.1%)	2 (5.0%)	1 (2.5%)	1 (2.4%)

Study ALT-801-211 MOMENTUM Obesity Trial, [1]rehydration for nausea and vomiting

Pemvidutide Phase 1b Trial in Patients with NAFLD

- Randomized, placebo-controlled study of pemvidutide in subjects with overweight/obesity and non-alcoholic fatty liver disease (NAFLD)
  - 12-week base study of 94 subjects randomized 1:1:1:1 to pemvidutide or placebo across 13 U.S. sites
  - 12-week extension study offered to subjects that completed 12 weeks of dosing (64 subjects participated in extension study for 24-weeks of total dosing)
  - No caloric restriction or lifestyle intervention
- Key Outcomes
  - Reduction in liver fat content, ALT and corrected T1 (cT1)



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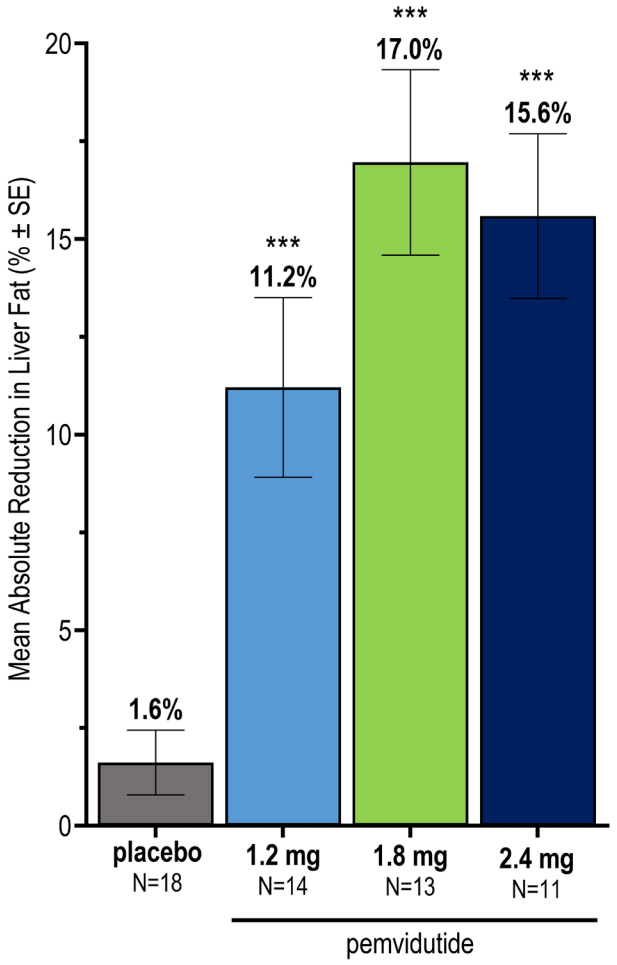
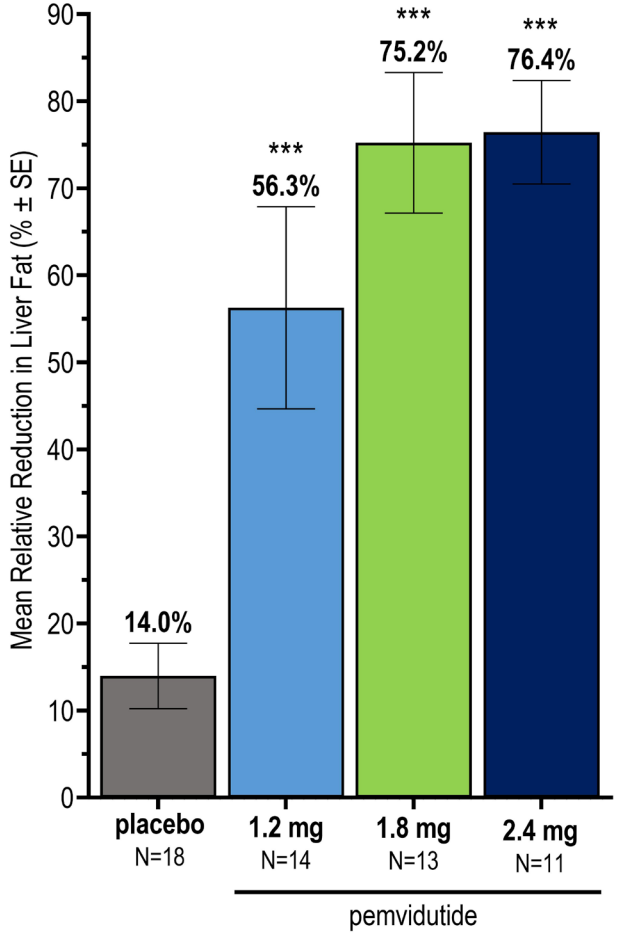
Pemvidutide— Robust Reduction in Liver Fat Content by MRI-PDFF at Week 24

Absolute Reduction



Relative Reduction



*** p < 0.001 vs. placebo, (ANCOVA)

Study ALT-801-106 NAFLD trial , Comparison to Week 0 (Baseline) of Study ALT-801-105, LS mean ± SE

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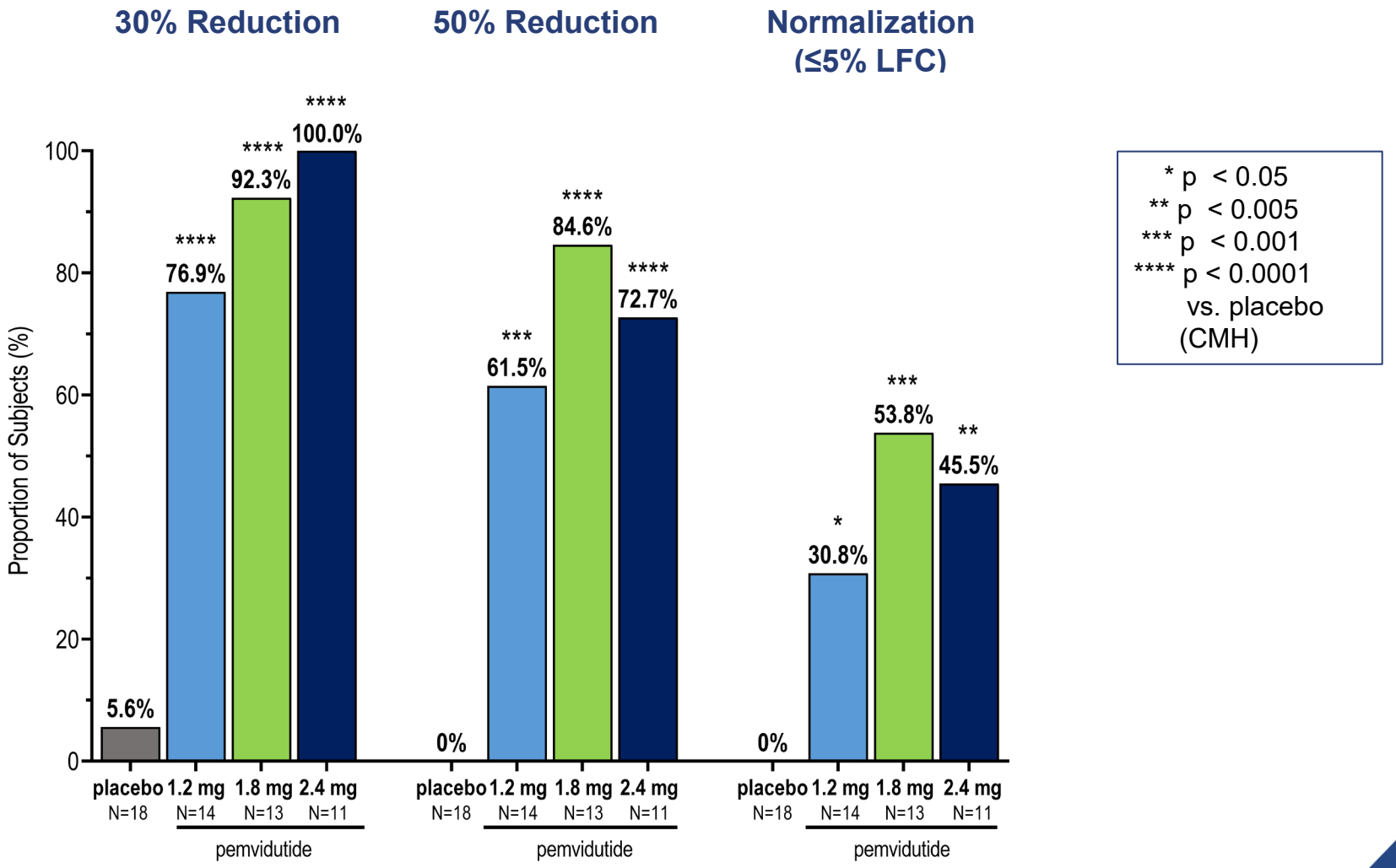
Pemvidutide— Robust Reduction in Liver Fat Content by MRI-PDFF Responder Analyses at Week 24



Study ALT-801-105 NAFLD Trial, Comparison to Week 0 (Baseline) of the Phase 1b NAFLD trial; CMH, Cochran-Mantel-Haenszel

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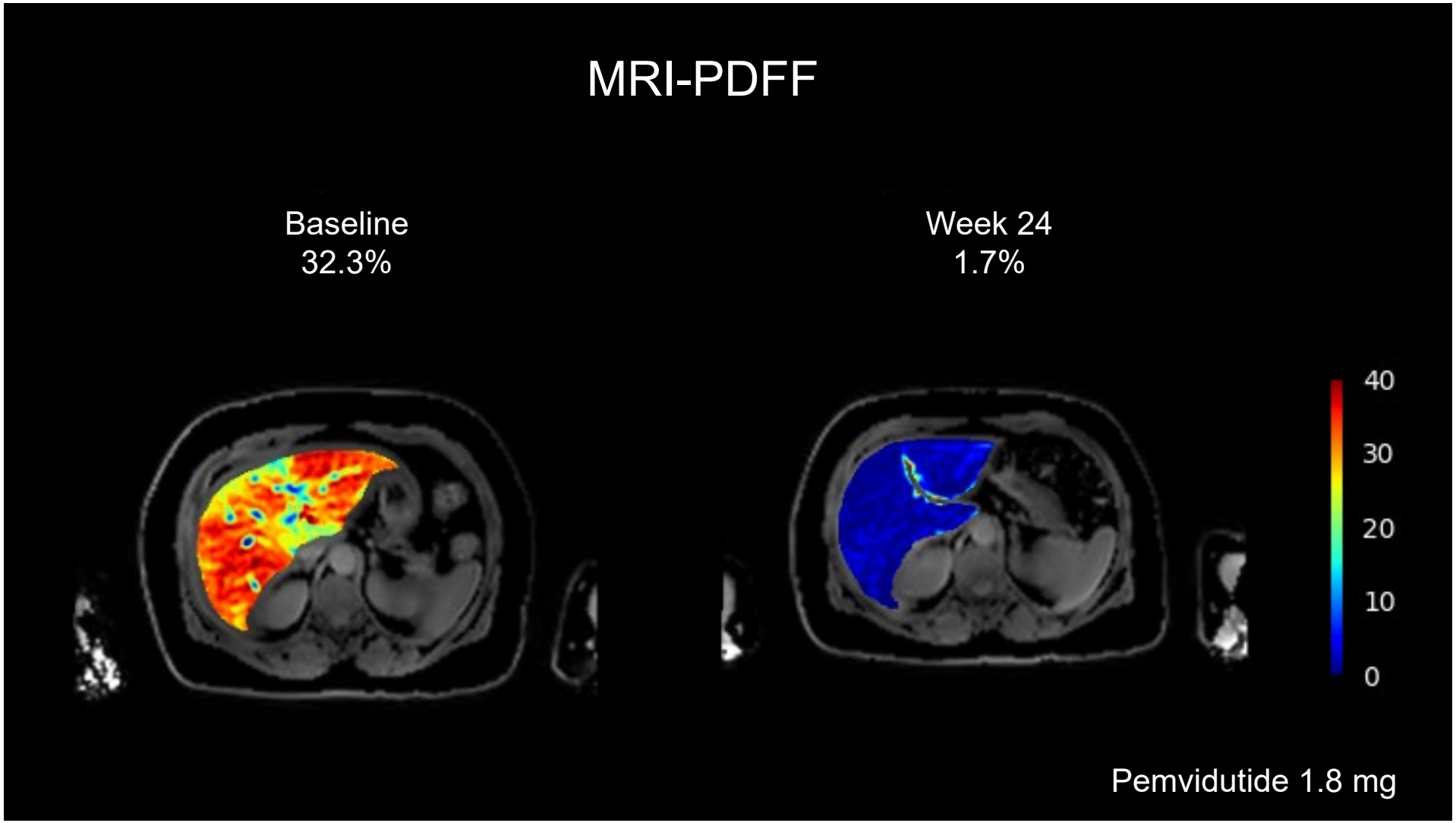
Pemvidutide— Marked Reduction of Liver Fat Content by MRI-PDFF at Week 24



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

Study ALT-801-106 NAFLD Trial

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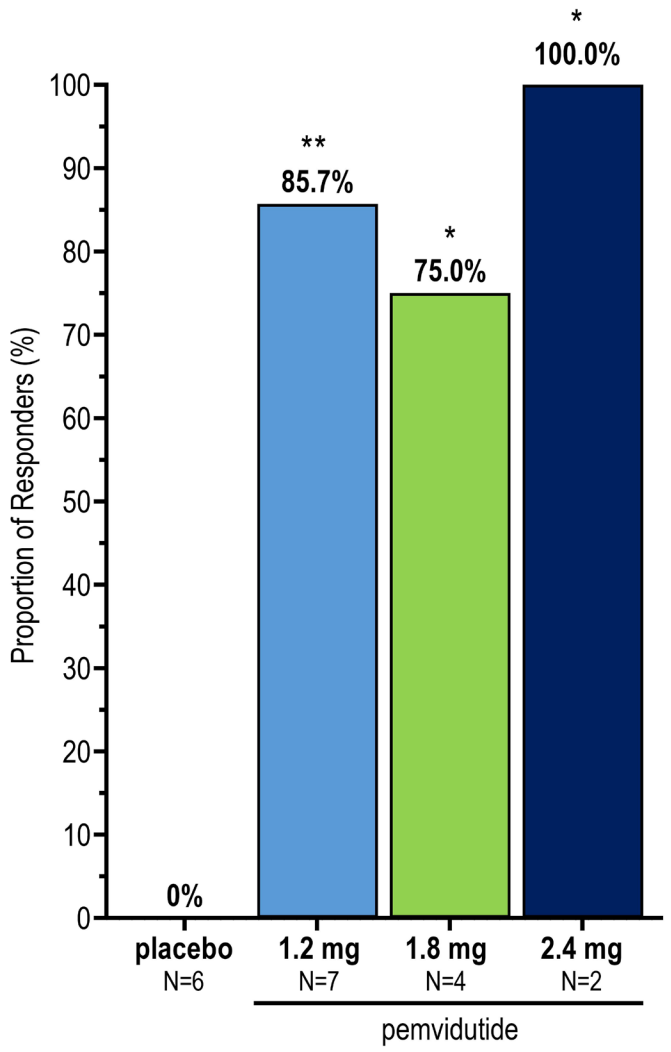
Pemvidutide— High Rates of cT1 Response at Week 24

RESPONSE DEFINED AS AN 80ms REDUCTION IN cT1 FROM BASELINE



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

- 80ms reduction in cT1 has been associated with a 2-point reduction of NASH Activity Score (NAS)[1]
- Elevated cT1 levels have been associated with increased risk of major adverse cardiac events (MACE) and major adverse liver outcomes (MALO)[2,3]

Study ALT-801-106 NAFLD Trial, comparison to Week 0 (Baseline) of the Phase 1b NAFLD trial; [1]Dennis A, Front Endocrinol 2021; [2]Jayaswal, A. Liver Int 2020; [3]Roca-Fernandez A, MedRxiv 2022;

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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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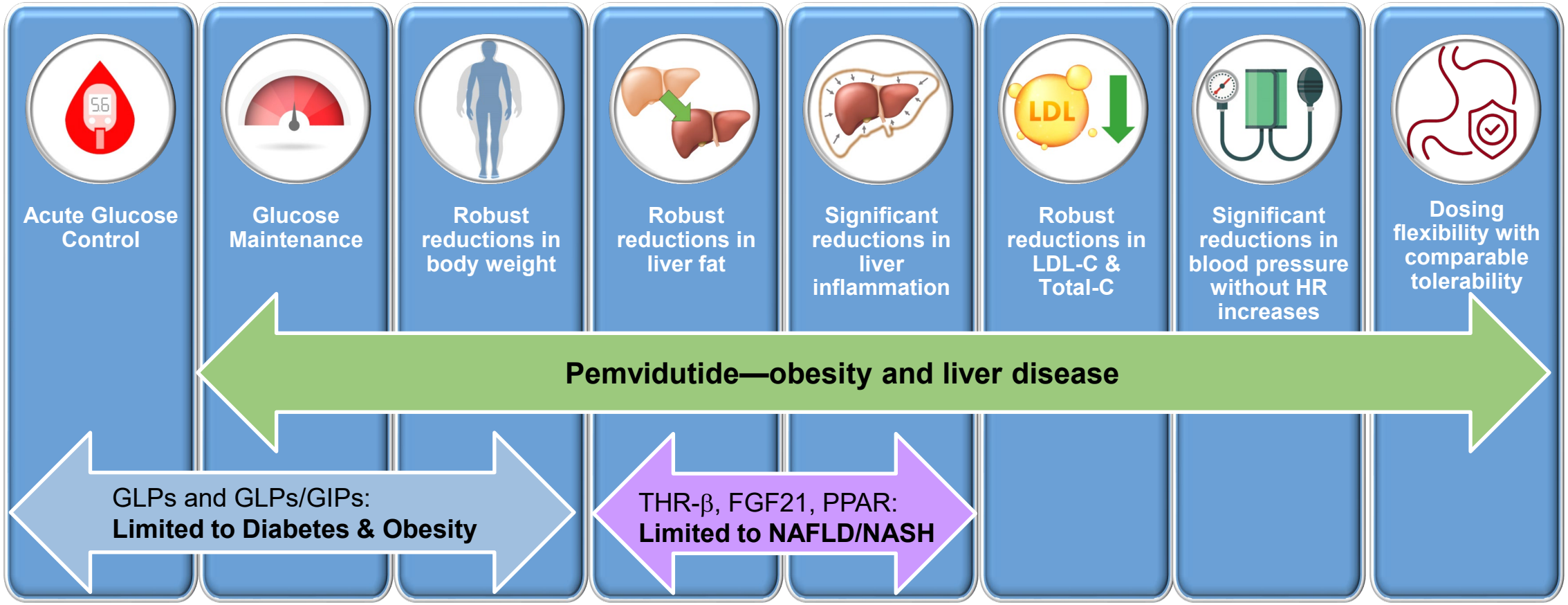
Pemvidutide—Differentiated with Broad Benefits



Thank you!

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