Pemvidutide, a GLP-1/Glucagon Dual Receptor Agonist, Significantly Reduces Liver Fat, Fibro-inflammation, and Body Weight in Patients with Non-alcoholic Fatty Liver Disease: a 24-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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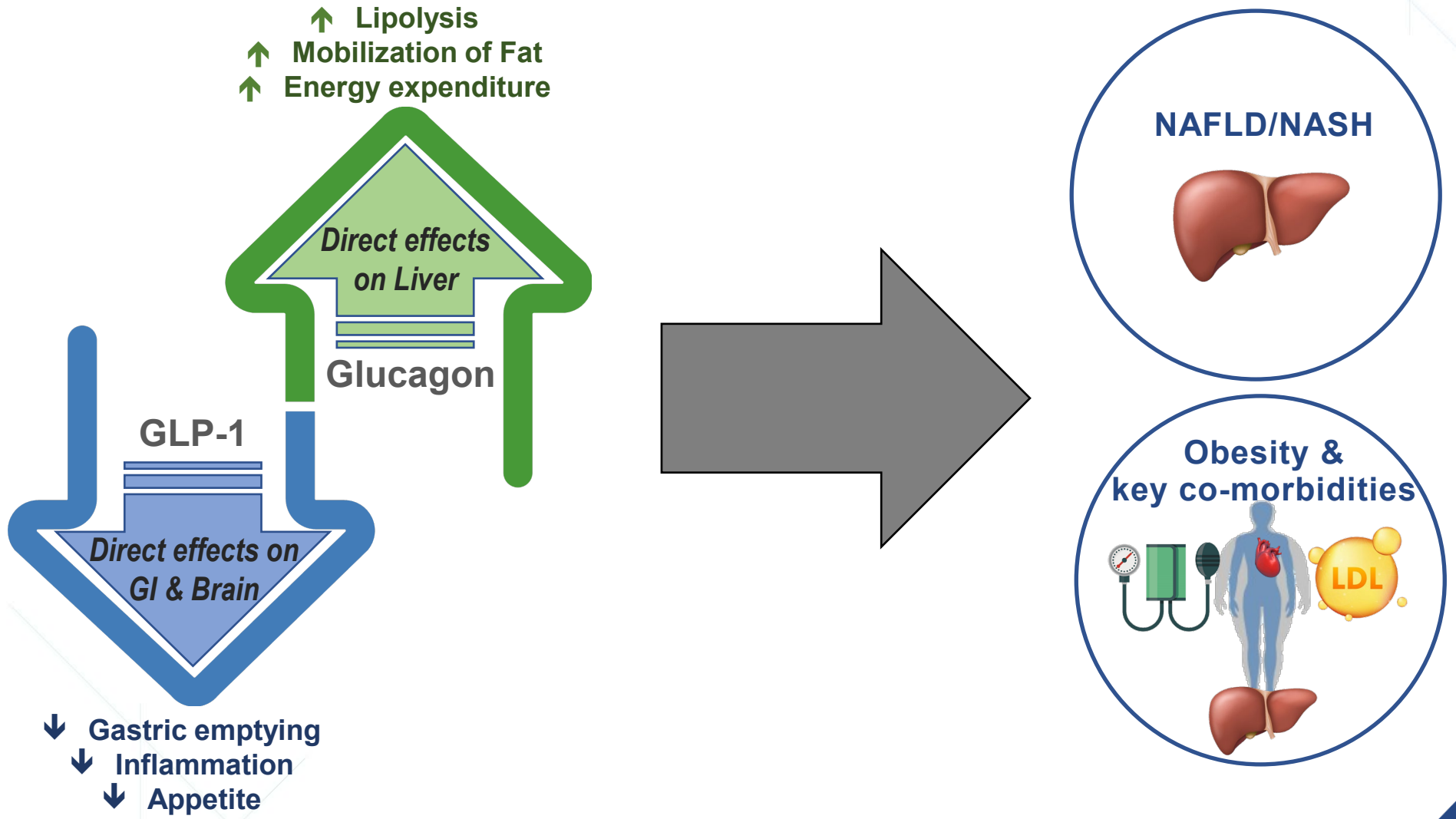
Disclosures

DISCLOSURES: I disclose the following financial relationship(s) with a commercial interest:

- Scientific advisor or consultant for Akero, Aligos, Altimmune, Arrowhead, Bluejay Therapeutics, Boxer Capital, Chronwell, Echosens, Enyo, Foresite Labs, Galectin, Galecto, Gilead, GSK, Hepagene, Hepion, Hepta Bio, HistoIndex, Humana, Intercept, Ionis, Madrigal, Medpace, NeuroBo Pharmaceuticals, Northsea, Novo Nordisk, Perspectum, Pfizer, Sonic Incytes, Sagimet, Terns, Viking.
- Stock options: Akero, Chronwell, Cirius, Galectin, Genfit, Hepion, Hepta Bio, HistoIndex, Metacrine, NGM Bio, Northsea, Sonic Incytes
- Grant/Research support: Akero, Altimmune, Axcella, BMS, Corcept, Cymabay, Enyo, Galectin, Genentech, Genfit, Gilead, GSK, Hepion, Hightide, Immuron, Intercept, Inventiva, Ionis, Madrigal, NGM Bio, Novartis, Novo Nordisk, Northsea, Pfizer, Poxel, Sagimet, Terns, Viking.

PEMVIDUTIDE: GLP-1/GLUCAGON DUAL RECEPTOR AGONIST

OPTIMIZED FOR TREATMENT OF NASH, OBESITY AND KEY CO-MORBIDITIES



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Pemvidutide 12 and 24-Week NAFLD Trial Design

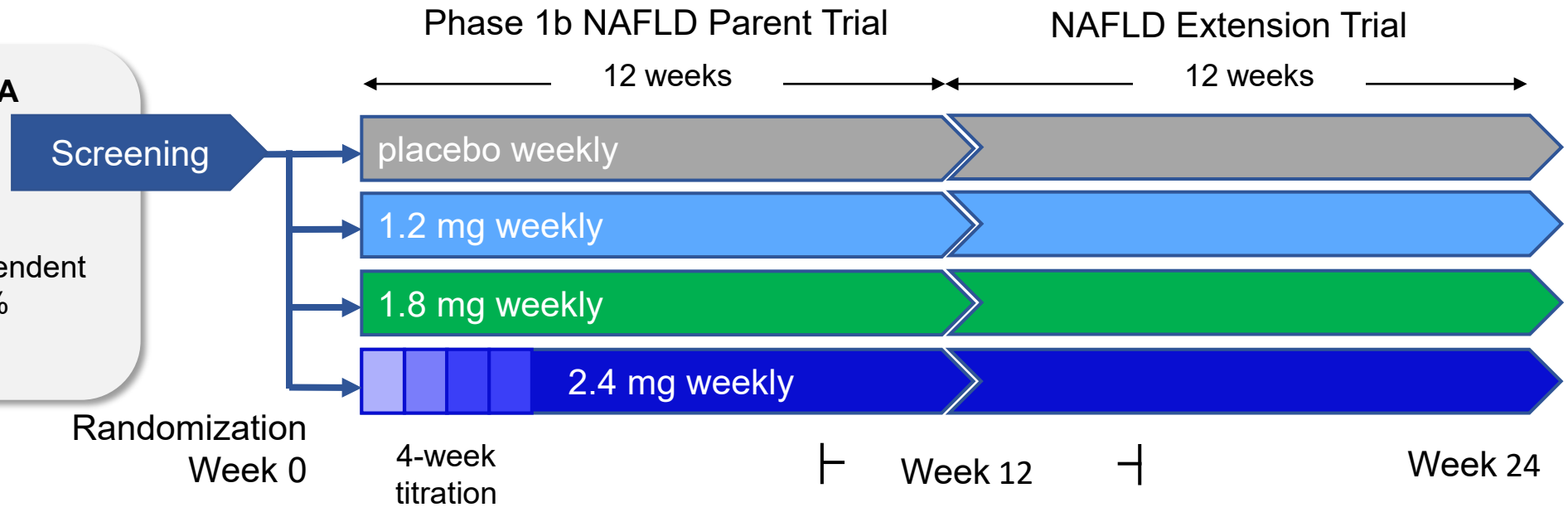
KEY ELIGIBILITY CRITERIA

MRI-PDFF ≥ 10%

FibroScan® LSM < 10kPa

Non-diabetes or non-insulin dependent diabetes with HbA1c< 9.5%

Serum ALT ≤ 75 IU/L



- Completers of the parent trial were invited to participate in a 12-week extension trial
- No adjunct caloric restriction or lifestyle intervention

Primary Endpoint

Reduction in liver fat content by MRI-PDFF at weeks 12 and 24

Secondary Endpoints

Reduction in hepatic fibro-inflammation (cT1), serum ALT, and body weight at weeks 12 and 24

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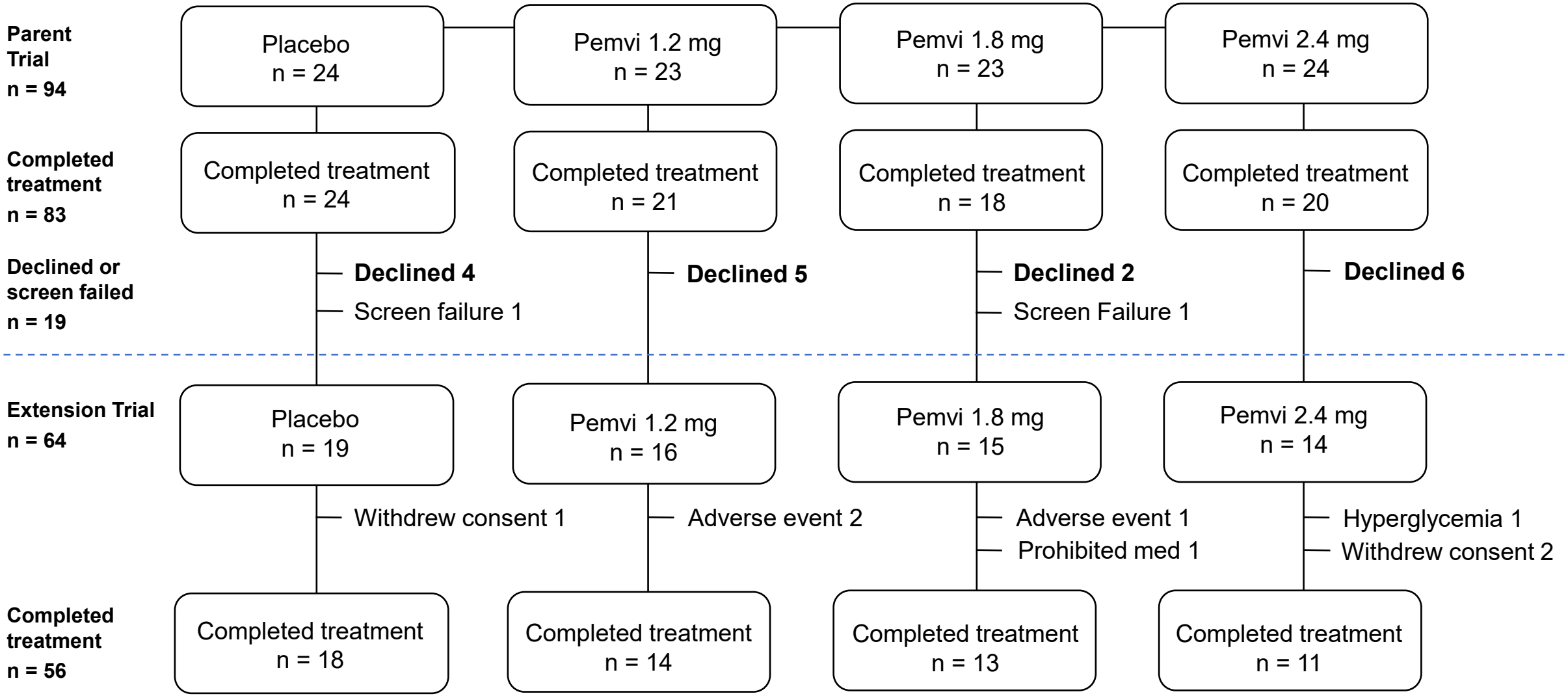
Trial Disposition



66 subjects consented to participate in the extension trial of whom 64 were eligible. Reasons for withdrawal of consent: Work conflicts (2), family obligations (1)

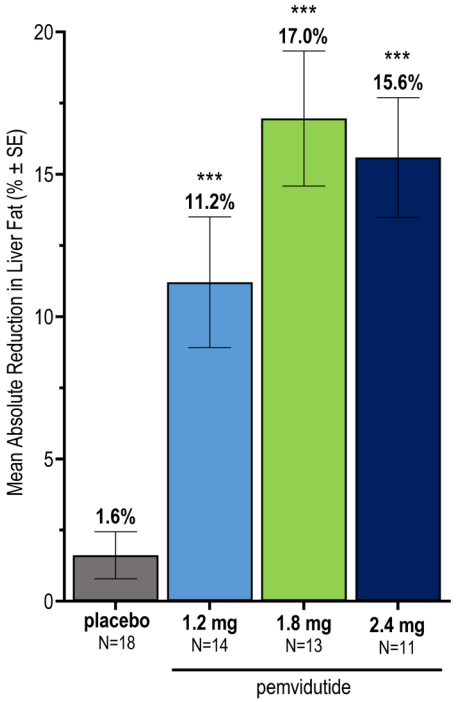
Extension Trial Population

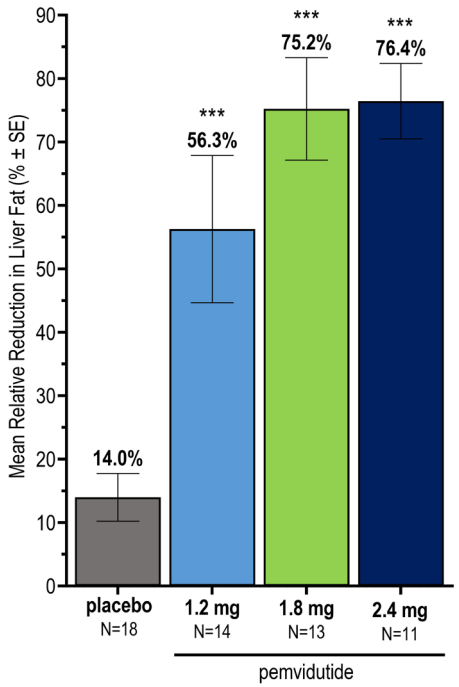
Baseline Characteristics		Treatment			
		Placebo (n = 19)	1.2 mg (n=16)	1.8 mg (n=15)	2.4 mg (n=14)
Age, years	mean (SD)	49.0 (15)	48.6 (11)	49.9 (10)	48.4 (8)
Gender	Female, n (%)	11 (57.9%)	7 (43.8%)	8 (53.3%)	8 (57.1%)
Ethnicity	Hispanic, n (%)	11 (57.9%)	15 (93.8%)	12 (80.0%)	9 (64.3%)
BMI, kg/m^2	mean (SD)	37.1 (4.9)	36.7 (6.1)	36.0 (3.8)	37.0 (5.3)
Body weight, kg	mean (SD)	104.4 (21.2)	101.4 (16.3)	100.9 (13.2)	107.4 (17.2)
Diabetes status	T2D, n (%)	5 (26.3%)	3 (18.8%)	6 (40.0%)	3 (21.4%)
HbA1c, %	mean (SD)	5.9 (0.4)	6.1 (1.0)	6.0 (0.5)	5.8 (0.8)
Serum AST, IU/L	mean (SD)	25.1 (10.5)	24.4 (6.7)	23.6 (6.9)	29.4 (15.5)
Serum ALT, IU/L	mean (SD)	41.0 (21.3)	32.4 (14.2)	35.3 (13.0)	39.6 (26.6)
Liver fat content, %	mean (SD)	24.0 (9.6)	20.1 (7.7)	23.9 (7.4)	20.5 (6.5)
Liver Volume, L	mean (SD)	2.3 (0.5)	2.3 (0.6)	2.5 (0.5)	2.3 (0.5)
cT1, ms	mean (SD)	933.4 (114.7)	892.1 (96.3)	909.4 (162.0)	933.7 (21.9)

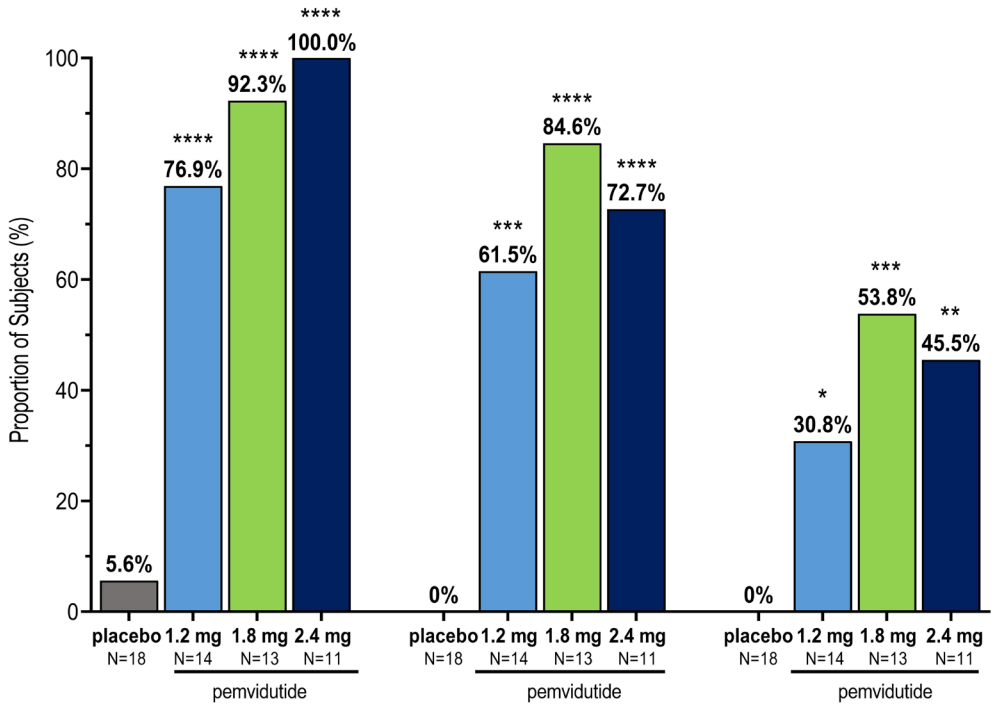
Baseline was defined as Week 0 of the parent Phase 1b NAFLD trial

Reduction in Liver Fat Content at Week 24

Absolute Reduction | **Relative Reduction** | **30% Reduction** | **50% Reduction** | **Normalization (<5%)**







Comparison to Week 0 (Baseline) of the parent Phase 1b NAFLD trial, LS mean ± SE
*** p < 0.001 vs. placebo, (ANCOVA)

* p < 0.05 ** p < 0.005 *** p < 0.001 **** p < 0.0001 vs. placebo, (Cochran-Mantel-Haenszel)

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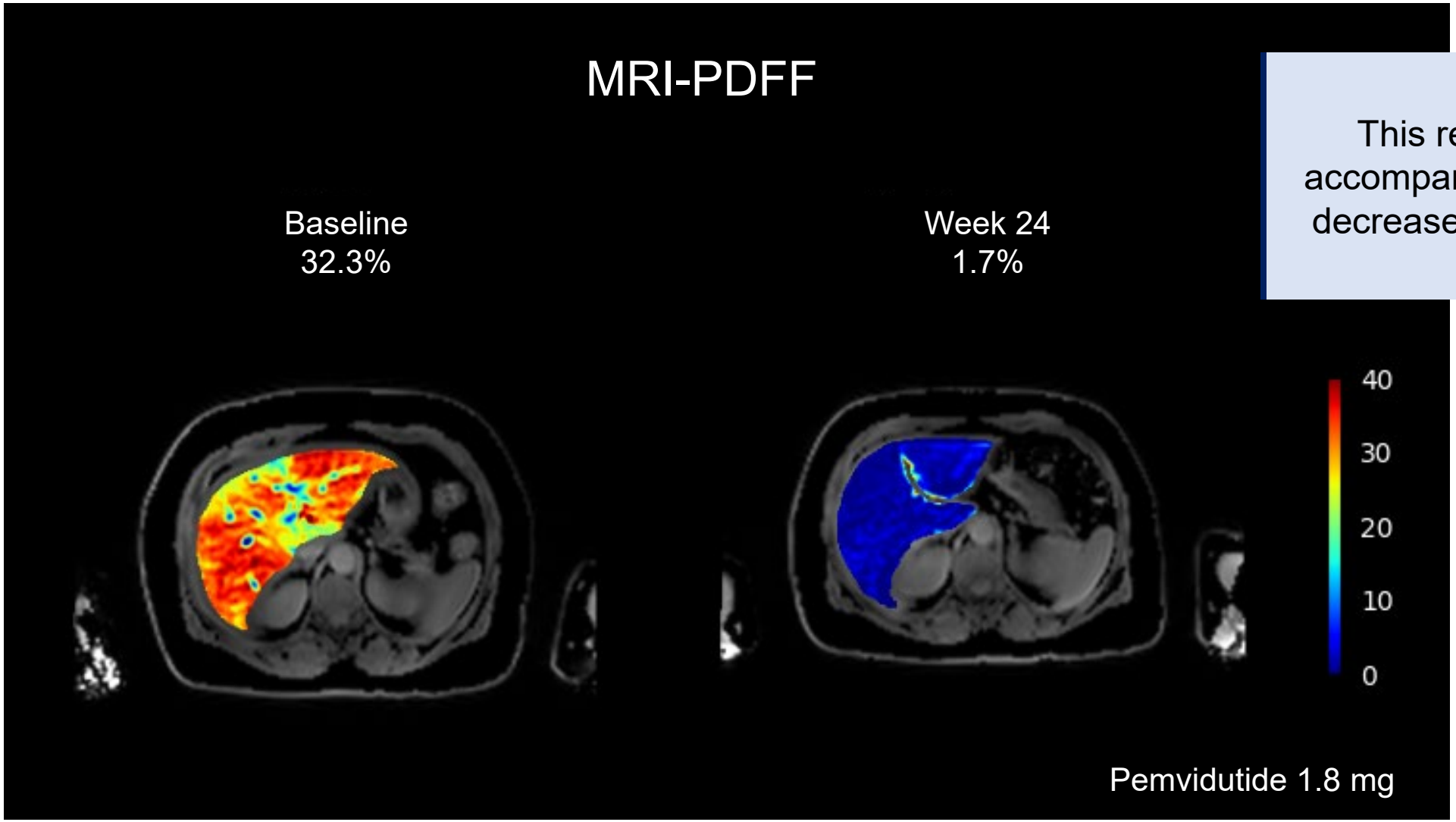
Marked Reduction in Liver Fat Content at Week 24



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

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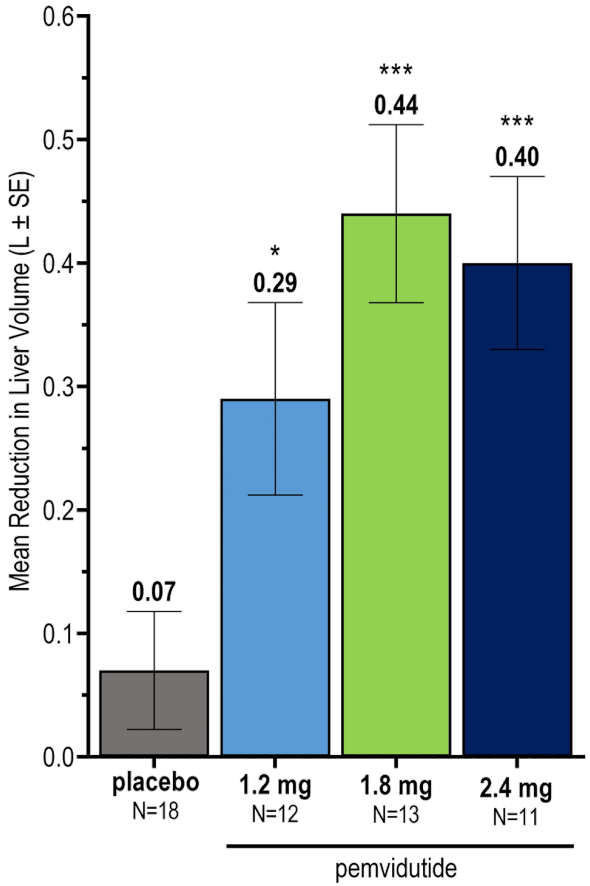
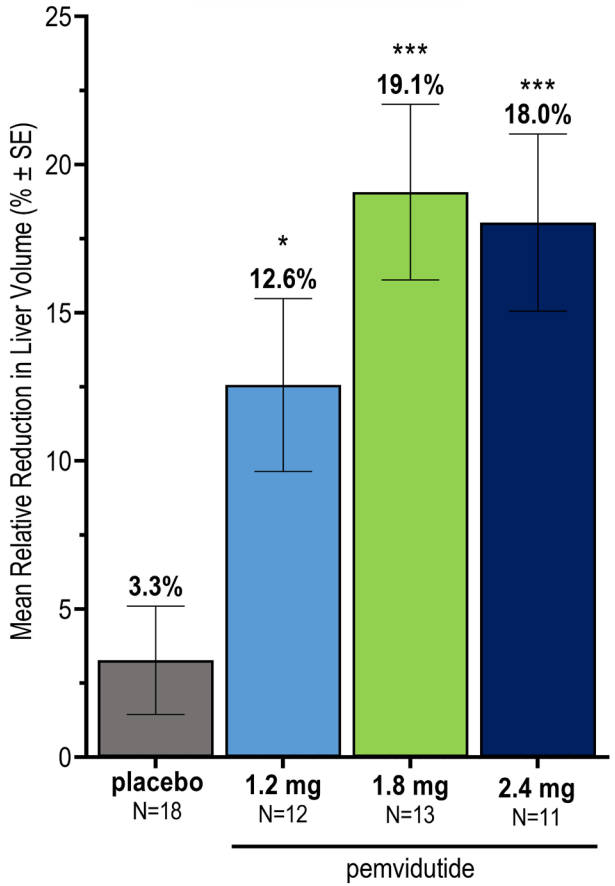
Reduction in Liver Volume at Week 24

Absolute Reduction



Relative Reduction



Comparison to Week 0 (Baseline) of the parent Phase 1b NAFLD trial, LS mean ± SE
* p < 0.05 *** p < 0.001 vs. placebo, (ANCOVA)

Liver Volume has been Associated with Overall Mortality

	All	
	HR (95%CI)	*P* value
Hepatic steatosis (Ultrasound)	1.15 (0.74; 1.62)	.483
Hepatic steatosis (MRI-PDFF)	0.94 (0.64, 1.39)	.762
Liver fat content (MRI %)	1.01 (0.98; 1.04)	.372
Liver volume (cm^3)	3.16 (1.88; 5.30)	<.001
Liver volume calc. from diameters (cm^3)	2.78 (1.76; 4.39)	<.001
FIB-4 score	1.42 (1.12; 1.78)	.003
ALT (IU/L)	1.07 (0.95; 1.20)	.256
AST (IU/L)	1.20 (1.06; 1.37)	.004
GGT (IU/L)	1.02 (1.01; 1.03)	<.001

Naeem M. Liver International. 2022;42:575-584

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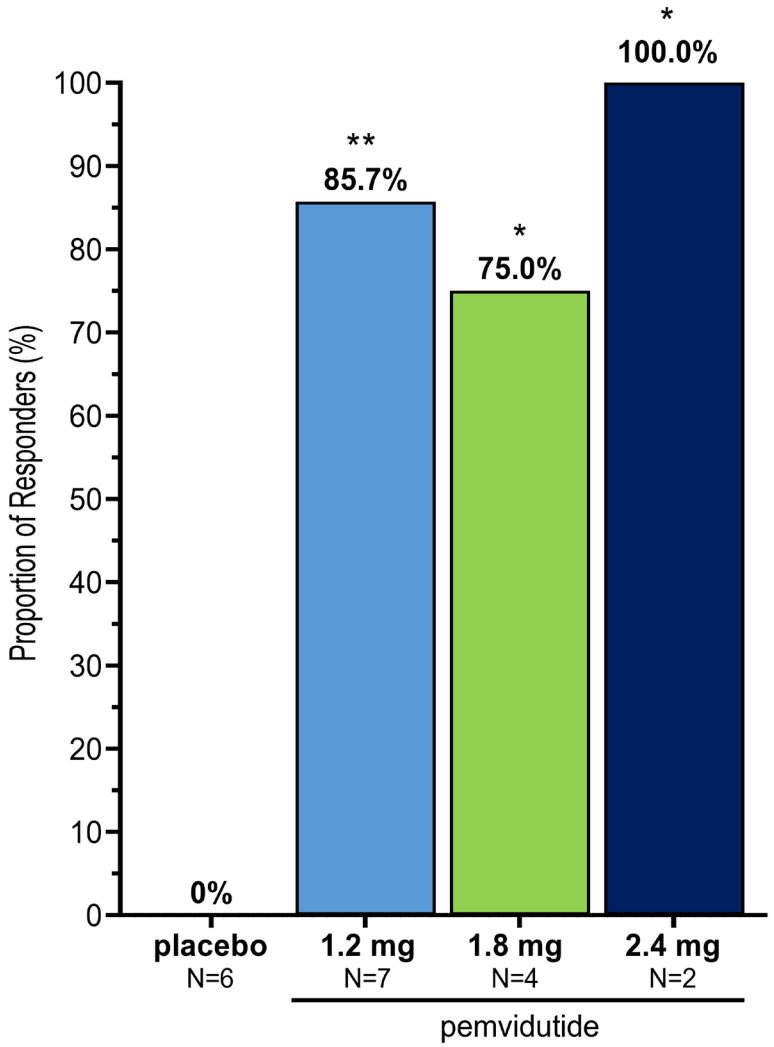
cT1 Responder Rates at Week 24

RESPONDER DEFINED AS A SUBJECT WITH ≥ 80ms[1] REDUCTION IN cT1 FROM BASELINE



Comparison to Week 0 (Baseline) of the parent Phase 1b NAFLD trial; [1]Dennis A, Front Endocrinol 2021

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

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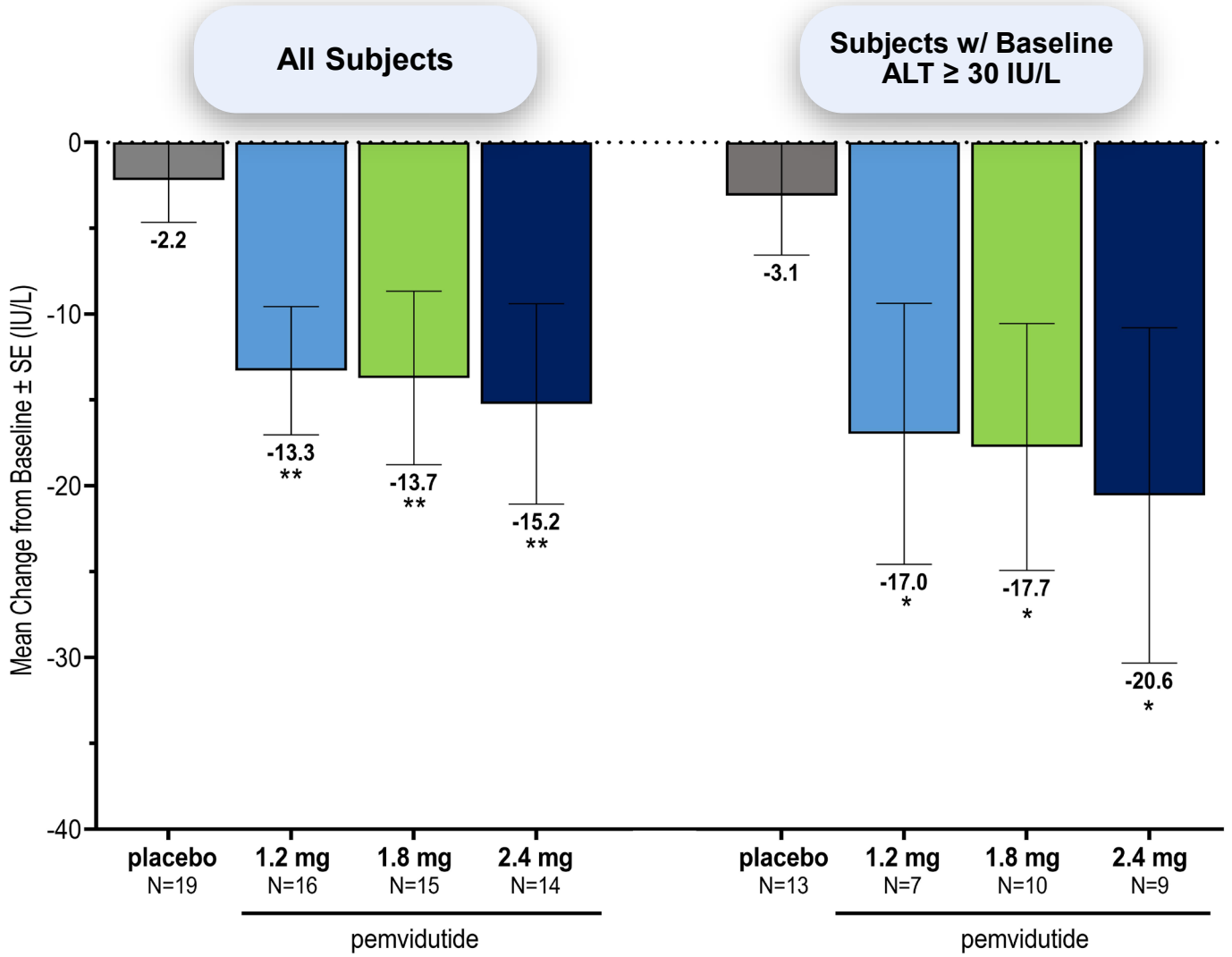
Changes in Serum ALT at Week 24



Comparison to Week 0 (Baseline) of the parent Phase 1b NAFLD trial; MMRM, mixed model with repeated measures, LS mean ± SE
* p < 0.05 ** p < 0.005 vs. placebo (MMRM)

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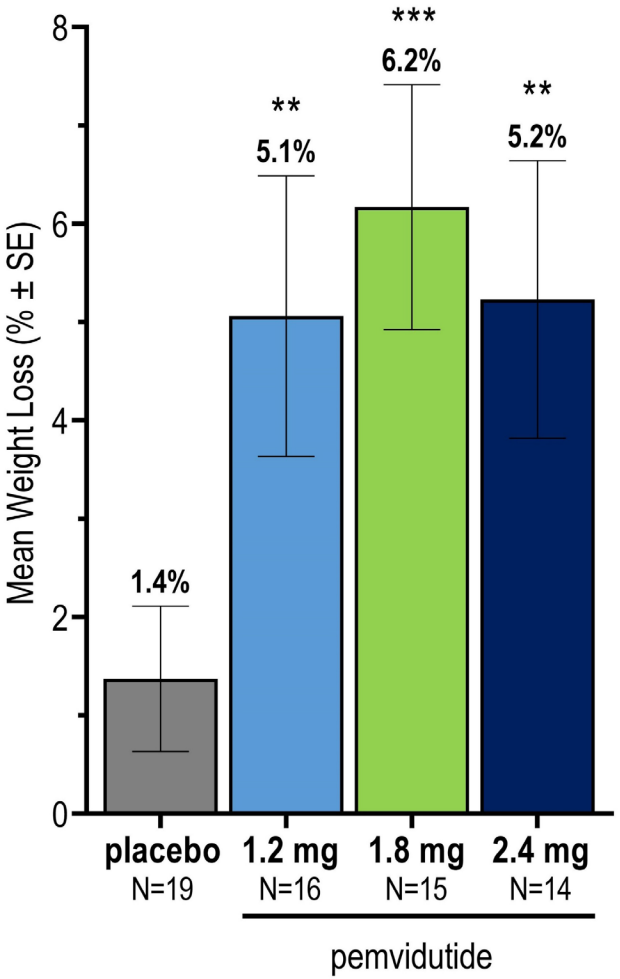
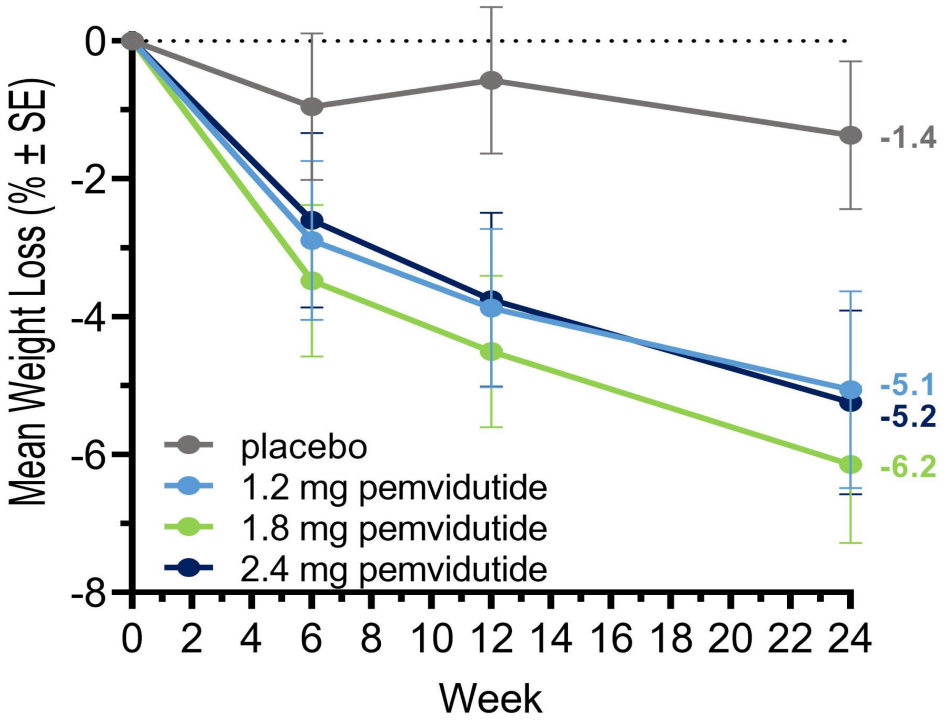
Weight Loss at Week 24

CONTINUING WEIGHT LOSS THROUGH END OF TREATMENT





Comparison to Week 0 (Baseline) of the Phase 1b NAFLD trial; MMRM, mixed model with repeated measures, LS mean ± SE
** p < 0.005 *** p < 0.001 vs. placebo (MMRM)

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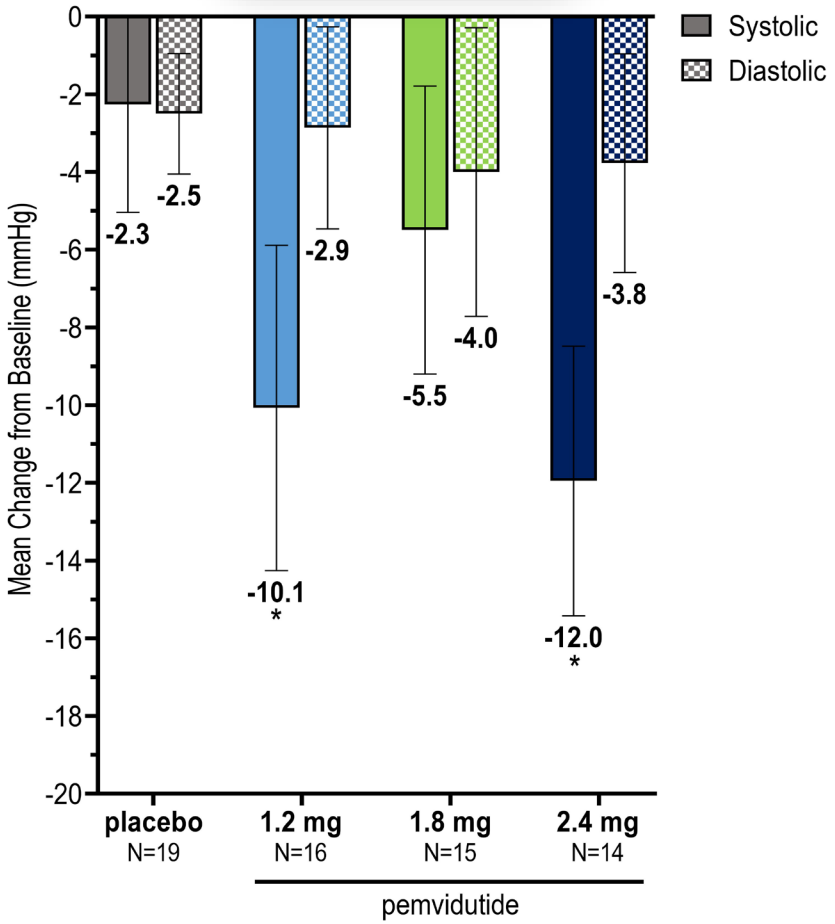
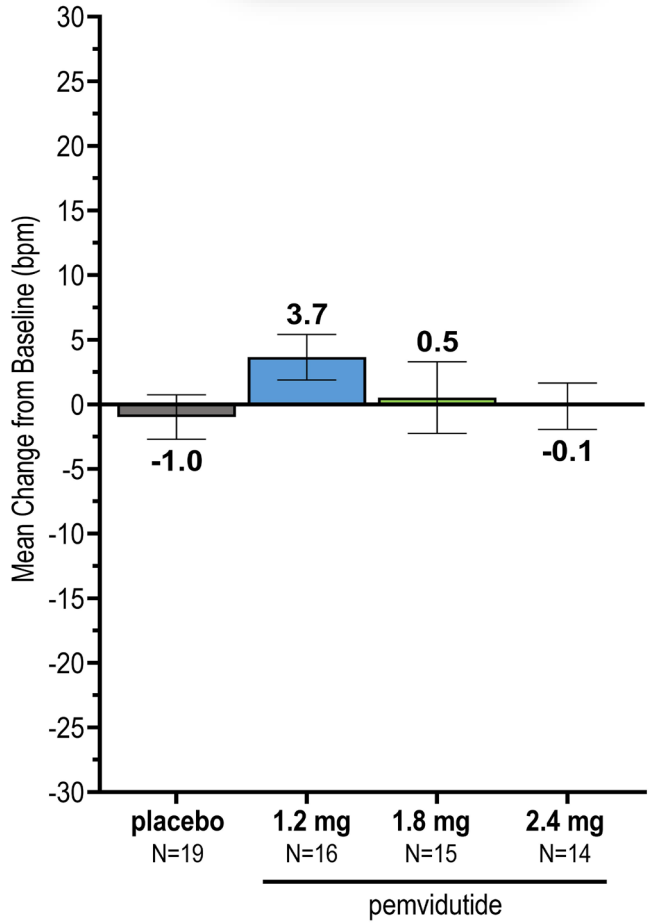
Improvements in Blood Pressure without Clinically Meaningful Increases in Heart Rate at Week 24

Blood Pressure



Heart Rate



Comparison to Week 0 (Baseline) of the parent Phase 1b NAFLD trial; MMRM, mixed model with repeated measures, LS mean ± SE
* p < 0.05 vs. placebo (MMRM)

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Changes in Serum Lipids at Week 24

Characteristic		Treatment			
		Placebo (n = 19)	1.2 mg (n=16)	1.8 mg (n=15)	2.4 mg (n=14)
Total cholesterol, mean (SD)					
Baseline	mg/dL	181.4 (35.7)	184.1 (46.8)	196.8 (38.6)	187.2 (36.0)
Week 24	mg/dL	169.4 (44.1)	170.9 (40.1)	173.2 (23.7)	162.0 (33.1)
LDL cholesterol, mean (SD)					
Baseline	mg/dL	97.8 (37.1)	95.5 (38.9)	110.6 (36.4)	104.8 (29.6)
Week 24	mg/dL	94.7 (43.7)	95.9 (31.8)	98.6 (26.1)	95.5 (30.9)
HDL cholesterol, mean (SD)					
Baseline	mg/dL	47.2 (7.3)	43.3 (10.2)	45.6 (8.4)	47.2 (6.7)
Week 24	mg/dL	44.9 (7.7)	42.2 (8.9)	41.4 (4.1)	43.3 (6.7)
Triglycerides, mean (SD)					
Baseline	mg/dL	182.5 (96.3)	232.1 (127.2)	217.0 (102.0)	209.9 (146.1)
Week 24	mg/dL	148.8 (78.9)	190.4 (177.0)	167.4 (94.5)	115.1 (37.6)

Baseline refers to Week 0 of the Phase 1b NAFLD trial

Glycemic Control at Week 24

Characteristic		Treatment			
		Placebo	1.2 mg	1.8 mg	2.4 mg
NON-DIABETES		N=14	N=13	N=9	N=11
Fasting glucose					
Baseline, mg/dL	mean (SD)	96.2 (12.4)	99.4 (11.9)	96.0 (12.4)	99.3 (13.6)
Week 24, mg/dL	mean (SD)	93.3 (12.1)	99.1 (13.1)	96.9 (12.5)	98.4 (24.5)
HbA1c					
Baseline, %	mean (SD)	5.8 (0.2)	5.7 (0.3)	5.7 (0.2)	5.5 (0.4)
Week 24, %	mean (SD)	5.7 (0.3)	5.8 (0.3)	5.8 (0.3)	5.6 (0.3)
DIABETES		N=5	N=3	N=6	N=3
Fasting glucose					
Baseline, mg/dL	mean (SD)	111.5 (19.2)	132.1 (28.2)	120.2 (37.1)	147.4 (40.4)
Week 24, mg/dL	mean (SD)	109.4 (14.8)	123.4 (50.8)	109.0 (13.1)	75.5 (29.0)
HbA1c					
Baseline, %	mean (SD)	6.1 (0.6)	7.8 (1.4)	6.4 (0.5)	6.8 (1.3)
Week 24, %	mean (SD)	6.4 (1.1)	7.4 (2.3)	6.4 (0.3)	6.3 (1.3)

Baseline refers to Week 0 of the parent Phase 1b NAFLD trial

Safety Overview—Extension Trial

Characteristic		Treatment			
		Placebo (n = 19)	1.2 mg (n=16)	1.8 mg (n=15)	2.4 mg (n=14)
Serious or severe AEs	n (%)	1 (5.3%)	1 (6.3%)	1 (6.7%)	0 (0.0%)
Related to treatment	n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs leading to treatment discontinuation	n (%)	0 (0.0%)	2 (12.5%)	1 (6.7%)	0 (0.0%)
Nausea					
Mild	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
Moderate	n (%)	0 (0.0%)	0 (0.0%)	3 (20.0%)	0 (0.0%)
Vomiting					
Mild	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diarrhea					
Mild	n (%)	1 (5.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)
Moderate	n (%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
Constipation					
Mild	n (%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)
Moderate	n (%)	1 (5.3%)	1 (6.3%)	0 (0.0%)	0 (0.0%)

1) chest pain post elective coronary stent placement (placebo), 2) Salmonella infection (pemvi 1.2 mg), and 3) hypertension >3 weeks post last dose of study medication (pemvi 1.8 mg), all unrelated to study treatment, with only the Salmonella infection leading to treatment discontinuation. The other AEs leading to treatment discontinuation were mild (Grade 1) abdominal pain in 2 subjects.

Summary and Conclusions

LIVER FAT REDUCTION

- Greater than 75% relative liver fat reduction at 24 weeks, better than or equal to the effects of other leading NASH candidates
- Significant reductions in liver volume, normalization in serum ALT and improvement in cT1 that correlate with liver fat reduction and point to potent effects in NASH clinical trials

WEIGHT LOSS

- 6.2% weight loss by Week 24 with continuing weight loss through end of treatment

FAVORABLE SAFETY/TOLERABILITY PROFILE

- No serious or severe AEs related to pemvidutide with low rates of AEs leading to treatment discontinuation
- Cardioprotective reductions in blood pressure without clinically meaningful increases in heart rate
- Glycemic control maintained with trends toward improvements in fasting glucose and HbA1c in subjects with diabetes

Thank you

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