As presented at AASLD 2024

Effect of Resmetirom or Placebo in NASH Fibrosis Patients With <5% or ≥5% Weight Loss and/or on Baseline GLP-1 Therapy in the MAESTRO-NASH 52-Week Serial Liver Biopsy Study

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Speaker Disclosures

- Dr Noureddin
  - Advisory boards: Altimmune, Boehringer Ingelheim, CytoDyn, 89bio, GSK, Madrigal, Merck, Novo Nordisk, NorthSea Therapeutics, Prespecturm, Terns, and Takeda
  - Principal investigator for a drug study: Allergan, Akero, Bristol Myers Squibb, Gilead Sciences, Galectin, Genfit, GSK, Conatus, Corcept, Enanta, Madrigal, Novartis, Novo Nordisk, Shire, Takeda, Terns, Viking, and Zydus
  - Stockholder: Rivus Pharma, CIMA, CytoDyn, and ChronWell

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Background

- MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled, phase 3 trial evaluating the **efficacy of resmetirom** in **patients with biopsy-confirmed NASH and fibrosis**
- A total of **966 patients** with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered orally once daily
- **Dual primary end points at Week 52 were achieved** with both resmetirom doses:
  - **NR**: NASH resolution (ballooning score=0, inflammation score=0/1, & ≥2-point reduction in NAS) with no worsening of fibrosis
  - **FI**: ≥1-stage improvement in fibrosis with no worsening of NAS
- Histologic end points were assessed after 52 weeks.

FI, fibrosis improvement' GLP-1, glucagon-like peptide-1; NASH, nonalcoholic steatohepatitis; NR, NASH resolution.

Background (cont)

- At baseline, 13% to 17% of patients in the treatment groups were on stable GLP-1 therapy (at least 6 months prior to randomization)
  - All patients taking GLPs in MAESTRO-NASH were diabetic
  - Multiple baseline GLPs were used at diabetes dosages
  - Other diabetic therapies associated with weight loss included SGLT2s

Aims:

In MAESTRO-NASH patients,

- The effects of resmetirom or placebo on GLP-1 baseline therapy were evaluated
- The effect of >=5% weight loss on liver biopsy end points with or without GLP-1 baseline therapy were evaluated

GLP-1 glucagon-like peptide-1.

Methods

KEY ELIGIBILITY CRITERIA

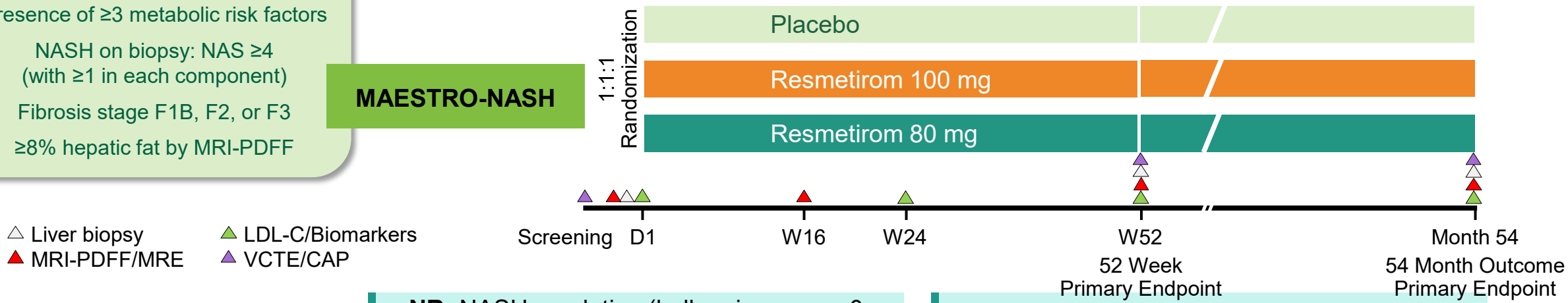
Presence of ≥3 metabolic risk factors

NASH on biopsy: NAS ≥4
(with ≥1 in each component)

Fibrosis stage F1B, F2, or F3

≥8% hepatic fat by MRI-PDFF

MAESTRO-NASH



DUAL PRIMARY END POINT AT WEEK 52

NR: NASH resolution (ballooning score=0, inflammation score=0/1, & ≥2-point reduction in NAS) with no worsening of fibrosis

FI: ≥1-stage improvement in fibrosis with no worsening of NAS

- Patients in this serial liver biopsy trial were counseled on moderate diet and exercise at each study visit
- Patients on baseline GLP-1 therapy with ≥5% weight loss at 52 weeks were evaluated for achievement of NR and FI liver biopsy end points or percent change from baseline in MRI-PDFF at Week 52

Harrison SA, et al. *N Engl J Med*. 2024;390(6):497-509.

CAP, controlled attenuation parameter; FI, fibrosis improvement; GLP-1 glucagon-like peptide-1; LDL-C, low-density lipoprotein-cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; NR, NASH resolution; VCTE, vibration-controlled transient elastography.

Baseline Characteristics

	No Diabetes	Diabetes		
	(N=319)	All Diabetes (N=647)	GLP-1 (N=137)	SGLT2 (N=130)
Age (years) – Mean (SD)	53.7 (12.3)	58.1 (9.9)	56.2 (9.2)	58.3 (8.6)
Female – n (%)	170 (53.3)	372 (57.5)	84 (61.3)	69 (53.1)
White n (%)	294 (92.2)	569 (87.9)	123 (89.8)	111 (85.4)
Hispanic or Latino – n (%)	63 (19.7)	141 (21.8)	23 (16.8)	30 (23.1)
Type 2 Diabetes – n (%)	0	647 (100.0)	137 (100.0)	130 (100.0)
Hypertension – n (%)	215 (67.4)	539 (83.3)	116 (84.7)	114 (87.7)
Dyslipidemia – n (%)	173 (54.2)	516 (79.8)	117 (85.4)	110 (84.6)
Thyroxine Replacement– n (%)	40 (12.5)	90 (13.9)	25 (18.2)	17 (13.1)
Statin Therapy – n (%)	97 (30.4)	376 (58.1)	84 (61.3)	86 (66.2)
Insulin Therapy – n (%)	0	118 (18.2)	44 (32.1)	38 (29.2)
Weight (kg) – Mean (SD)	101.5 (22.8)	100.3 (22.7)	103.7 (24.3)	99.7 (22.4)
BMI (kg/m^2) – Mean (SD)	35.4 (6.8)	35.8 (6.8)	36.6 (6.9)	35.4 (6.1)
HOMA-IR – Mean (SD)	9.4 (8.8)	12.0 (11.7)	12.9 (12.0)	9.3 (5.9)
HbA1c (%) – Mean (SD)	5.7 (0.6)	7.0 (1.0)	7.1 (1.0)	7.2 (1.0)
10-year ASCVD Risk Score – Mean (SD)	9.5 (7.4)	17.5 (12.7)	14.5 (10.8)	16.0 (10.6)
ELF – Mean (SD)	9.7 (0.9)	9.8 (0.9)	9.5 (0.8)	9.7 (0.8)
FibroScan VCTE (kPa) Median (Q1, Q3)	11.0(9.1, 14.6)	12.0(9.7, 15.5)	12.0(9.8, 15.5)	11.2(9.6, 13.9)
FibroScan CAP (dB/m)– Mean (SD)	342.1 (39.6)	350.3 (36.4)	351.8 (36.2)	348.8 (36.1)
(%) MRI-PDFF– Mean (SD)	18.4 (7.0)	17.4 (6.6)	16.5 (6.0)	16.1 (6.5)
MRE (kPa)– Median (Q1, Q3)	3.3(2.7, 3.9)	3.5(2.9, 4.2)	3.4(3.0, 4.0)	3.4(3.0, 4.1)
ALT (U/L) – Mean (SD)	62.1 (36.1)	52.1 (29.0)	45.6 (22.6)	48.3 (23.6)
AST (U/L) – Mean (SD)	45.7 (25.9)	38.8 (21.1)	34.3 (16.6)	34.7 (14.3)
NAS at Screening, ≥5 n (%)	263 (82.4)	544 (84.1)	110 (80.3)	101 (77.7)
Fibrosis Stage – n (%)				
1B	16 (5.0)	33 (5.1)	6 (4.4)	4 (3.1)
2	130 (40.8)	189 (29.2)	35 (25.5)	37 (28.5)
3	168 (52.7)	415 (64.1)	93 (67.9)	88 (67.7)
4	5 (1.6)	10 (1.5)	3 (2.2)	1 (0.8)

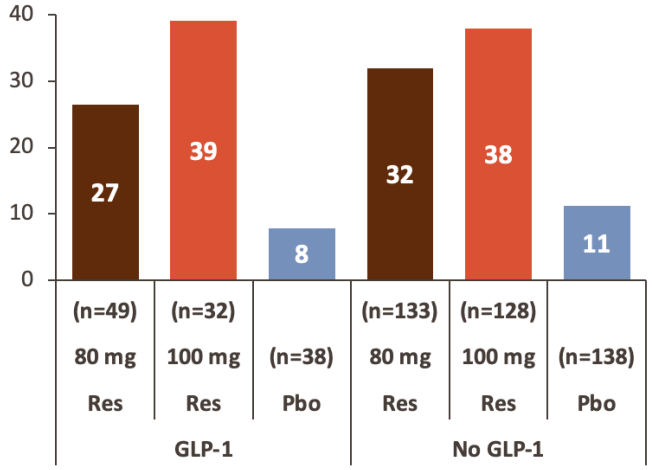
Baseline Characteristics

- In MAESTRO-NASH, baseline GLP-1 therapy had been in place for >6 months,
- All patients on GLP therapy had diabetes; the most common dose was 1 mg semaglutide or comparable (dulaglutide)
- At baseline, patients on GLP-1 therapy had a higher % F3 with more metabolic and CV features, more common statin use, and, at baseline, lower LDL and liver enzymes than non-diabetic patients
- Patients on GLPs showed no difference in baseline MRI-PDFF or body weight
- There were no meaningful differences in baseline characteristics between the patient populations on SGLT2 therapy and/or GLP therapy

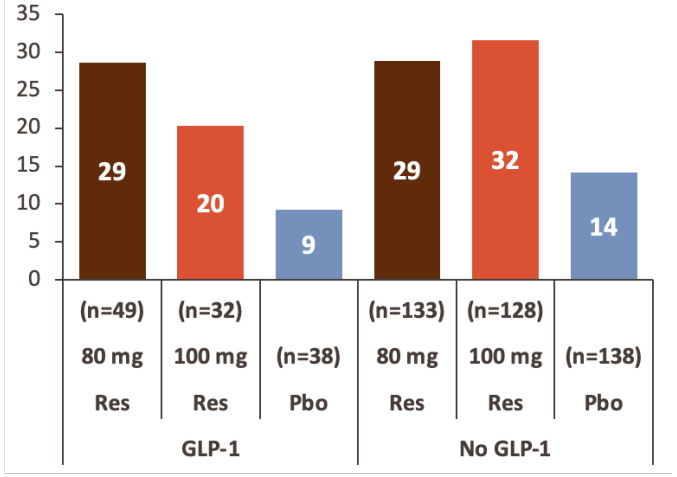
ELF, Enhanced Liver Fibrosis test; FIB-4, Fibrosis-4 Index; GLP-1, glucagon-like peptide-1; HbA1C, hemoglobin A1C; MRI-PDFF, magnetic resonance imaging-proton density fat fraction.

GLPs and SGLT2: No Impact on Biopsy Responses to Resmetirom

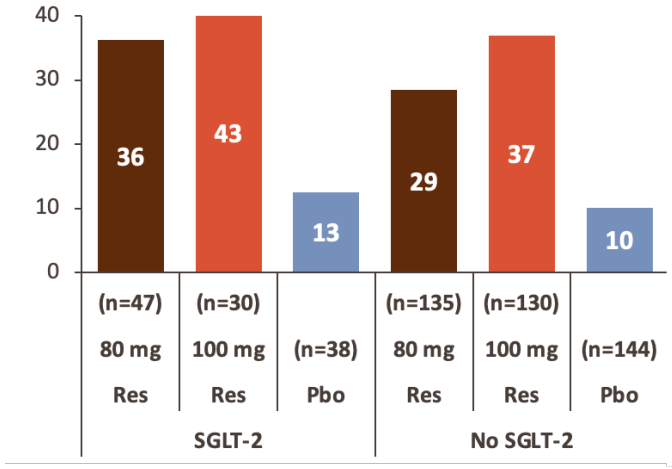
NASH Resolution GLP/no GLP



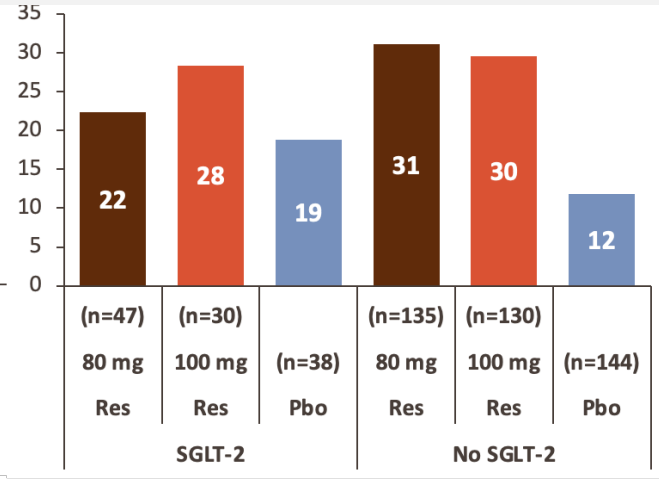
Fibrosis Improvement GLP/no GLP



NASH Resolution SGLT/no SGLT



Fibrosis Improvement SGLT/no SGLT



- Patients with diabetes on resmetirom plus SGLT2 or GLP-1 therapy had equivalent liver biopsy responses to patients with diabetes not on these therapies
- There were no differences in safety or tolerability in patients with diabetes treated with a combination of GLP-1 plus resmetirom

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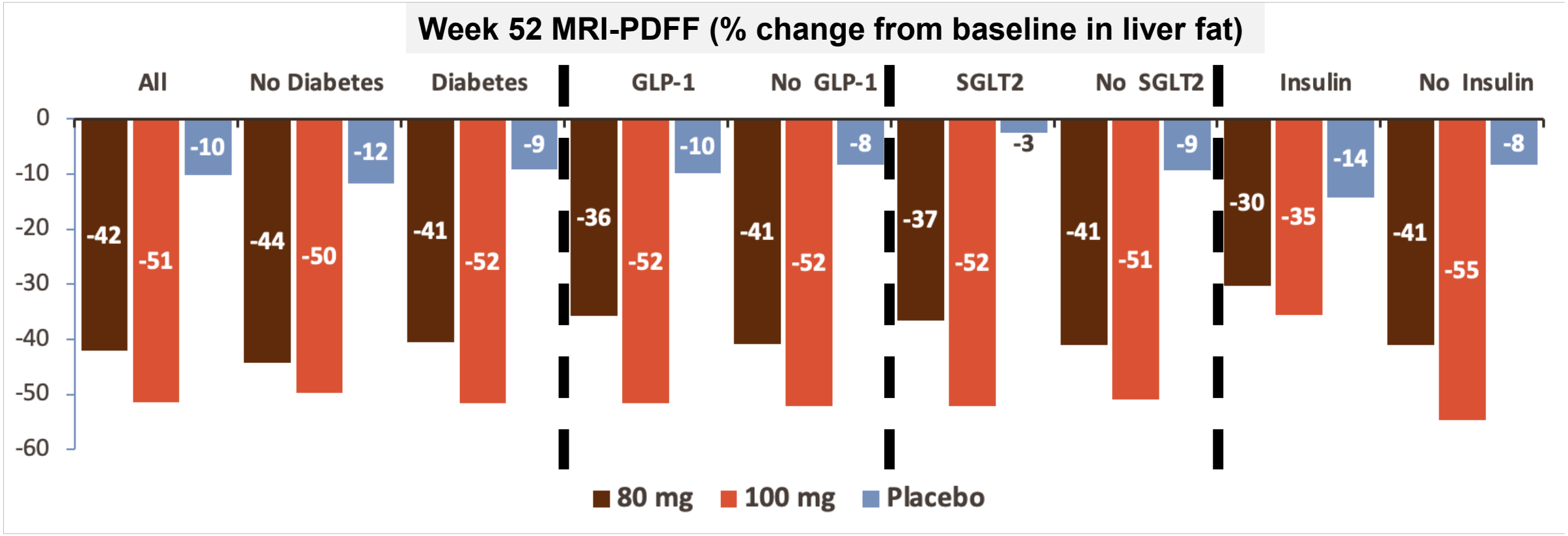
Various Diabetes Treatments Did Not Impact MRI-PDFF Reduction by Resmetirom



- The same response to PDFF-reduction with resmetirom was observed in patients with diabetes exposed to resmetirom and various treatments, including GLPs, SGLT2i or insulin

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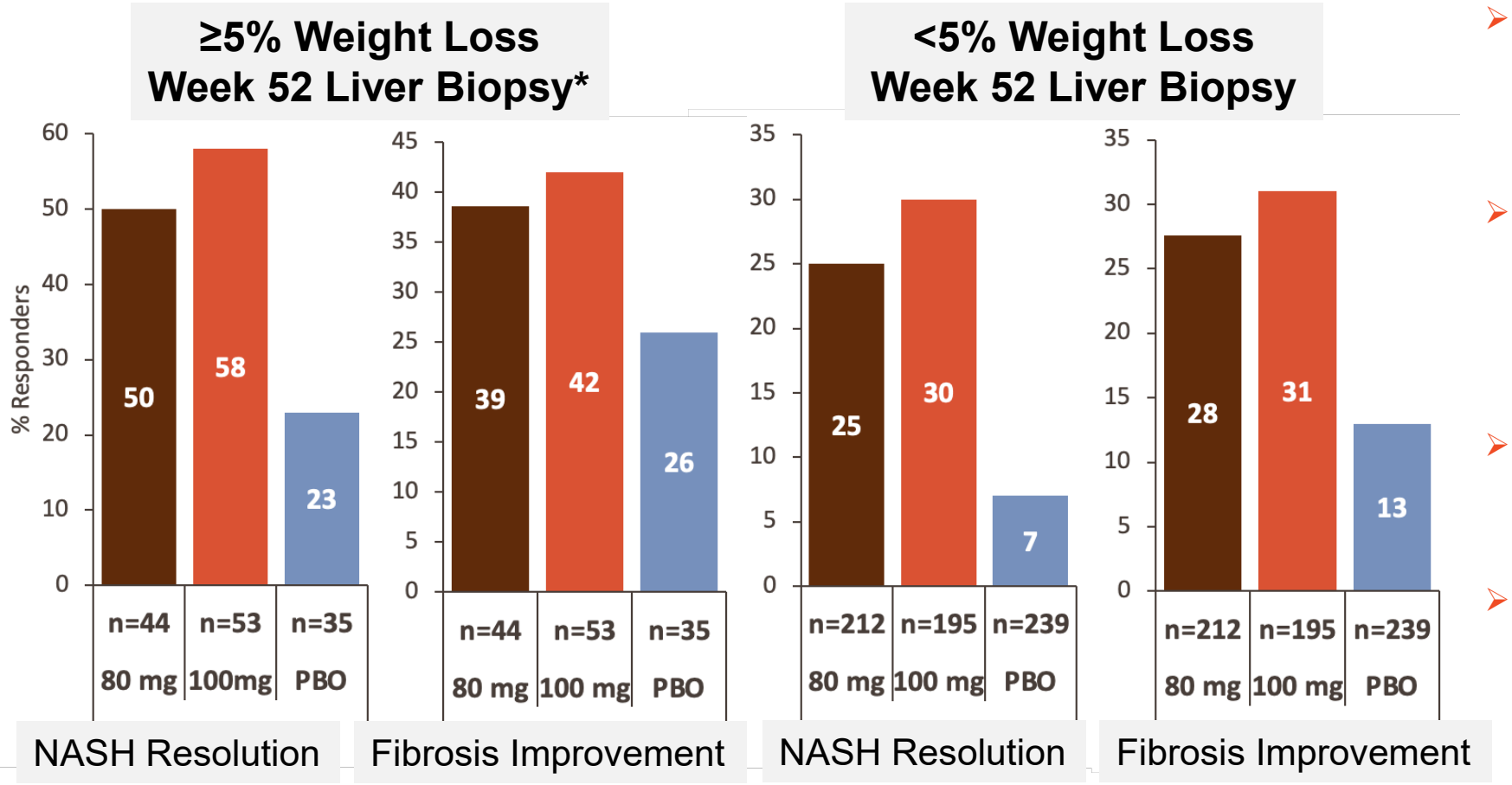
Weight Loss In MAESTRO-NASH

- 17% on 80 mg and 22% on 100 mg in the resmetirom arms achieved ≥5% weight loss at Week 52 compared with 12% on placebo
  - Higher weight loss with resmetirom that was statistically significant (nominal)
  - Median weight loss 7% in the ≥5% weight loss groups

- GLP-1 treatment in MAESTRO-NASH was not associated with weight loss:
  - 14% of patients with ≥5% weight loss were on GLP-1 receptor agonists
  - 15% of patients with <5% weight loss were on GLP-1 receptor agonists

Weight Loss/Resmetirom Impact on Biopsy Endpoints



- Weight loss ≥5% achieved by diet and exercise occurred in about 22% of patients on resmetirom (12% of placebo patients)
- In resmetirom 100mg arm, ≥5% weight loss was associated with increased fibrosis improvement (42%) and NASH resolution (58%) on liver biopsy; similar improvements in 80 mg arm
- ~3X more resmetirom than placebo patients with ≥5% weight loss had NR or FI
- Resmetirom maintained the favorable difference from placebos on NASH and fibrosis endpoints with all weight changes (no weight change, ≥5% weight loss or ≥5% weight gain)

Patients with Week 52 weight loss data and biopsy; consensus biopsy review

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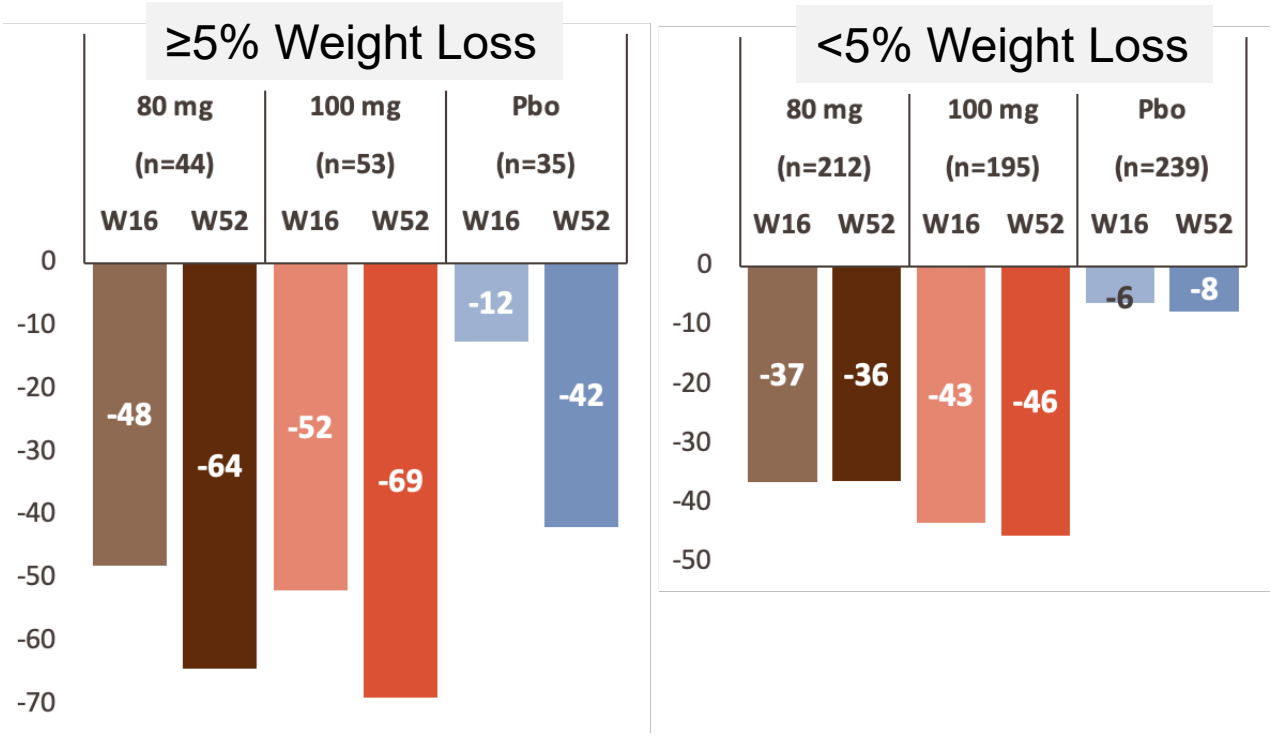
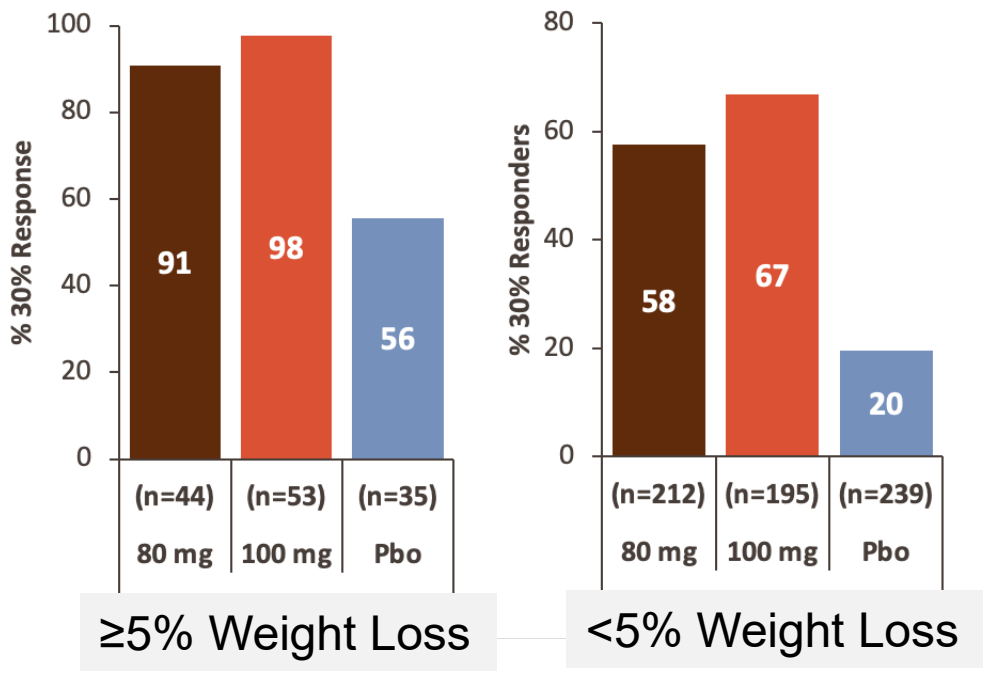
Weight Loss Effect on MRI-PDFF

MRI-PDFF % Reduction from Baseline at Week 16 and Week 52



MRI-PDFF % of Patients with ≥30% Reductions at Week 52



- PDFF-reduction in patients with ≥5% weight loss improved at Week 52 relative to Week 16; no change between Week 16 and Week 52 in patients without weight loss
- Resmetirom retains separation from placebo in both groups
- In resmetirom arm, 98% with ≥5% weight loss had a 30% PDFF response

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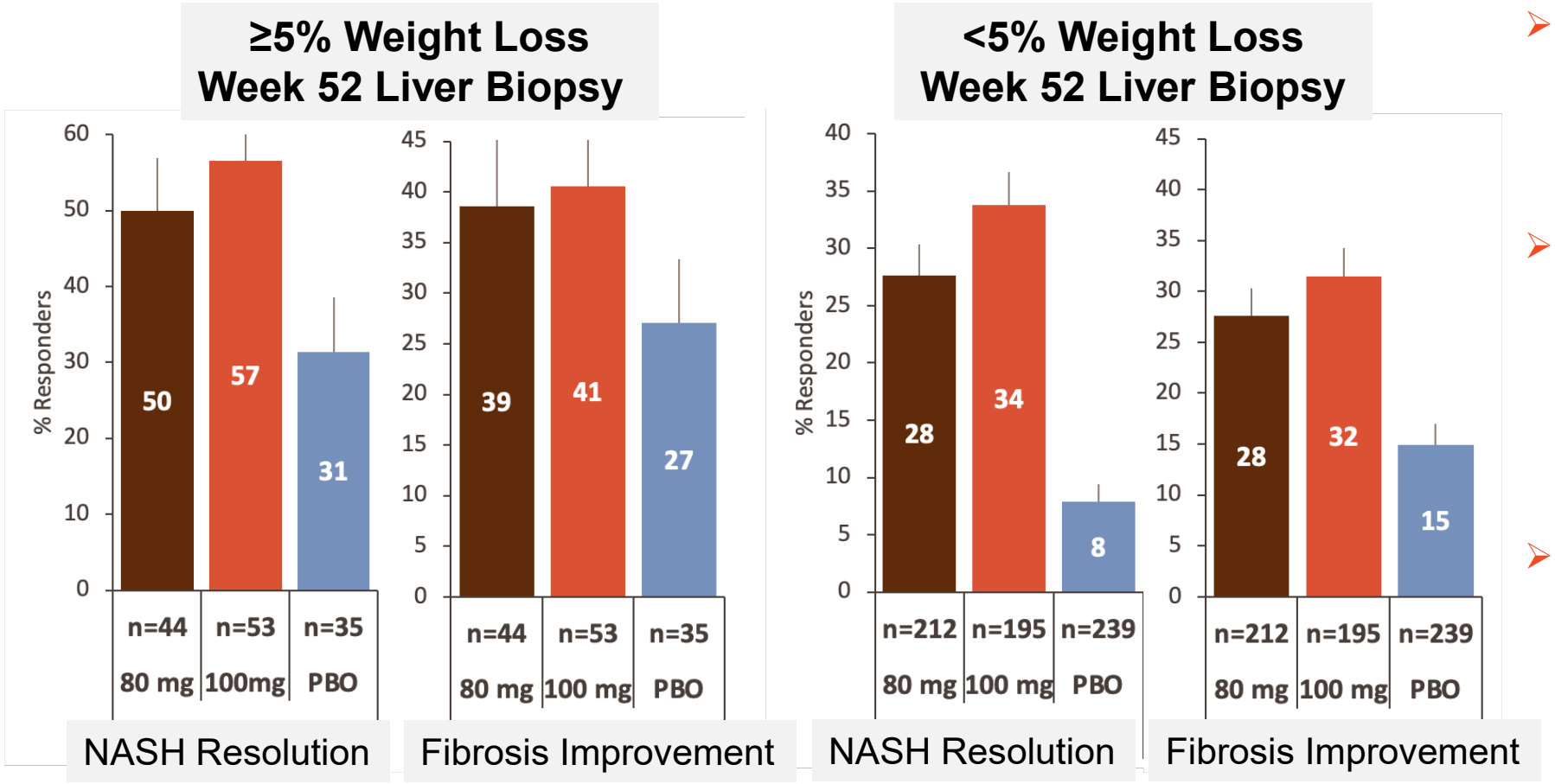
Summary

- In MAESTRO-NASH two thirds of patients had diabetes and many were stably treated with SGLT2i and GLP-1 RA therapy
- No weight loss above background occurred with GLPs given chronically
- GLP-1 RA and SGLT2i treated patients with diabetes showed the same NASH resolution and fibrosis improvement rates in combination with resmetirom as patients with diabetes not on these agents
- ≥5% weight loss was observed more frequently in resmetirom as compared with placebo treated patients
- ≥5% weight loss was associated with high rates of NASH resolution ~60% and fibrosis improvement ~40% in resmetirom-treated patients
- Relatively small amounts of weight loss enhance the effects of resmetirom on NASH and liver fibrosis

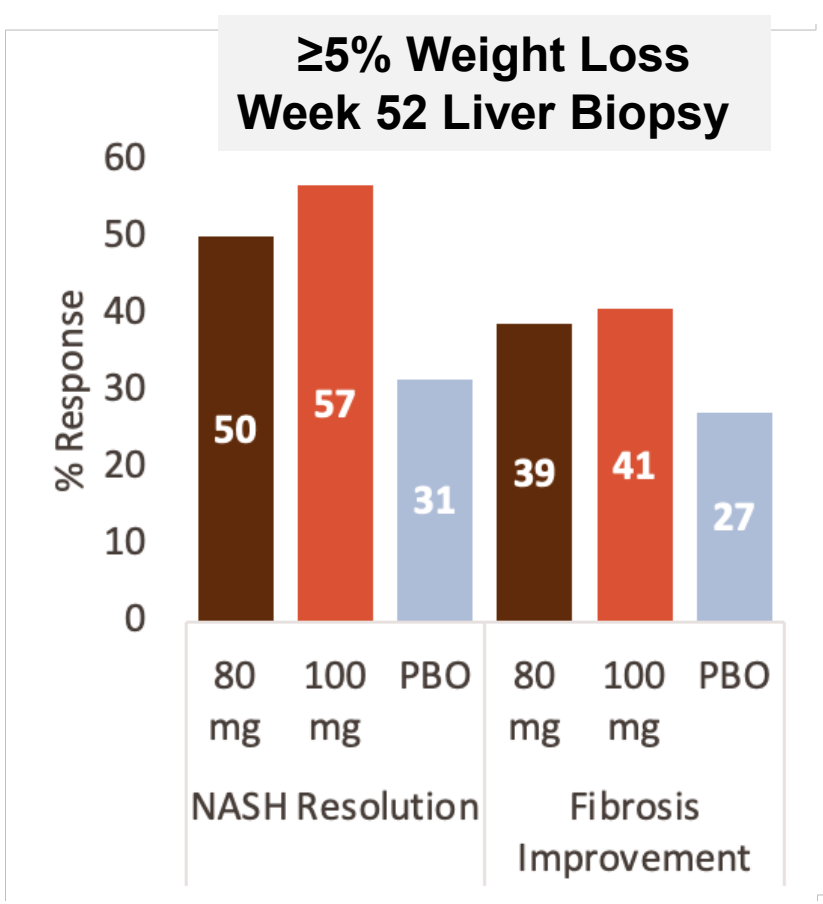
Backup

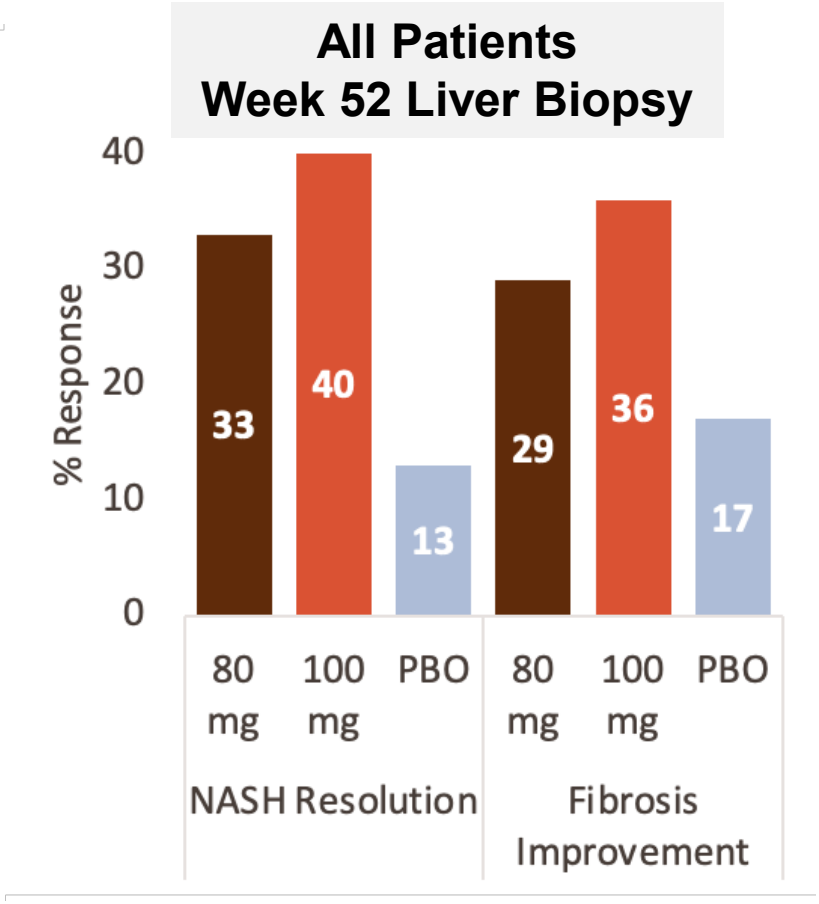
Weight Loss/Resmetirom Impact on Biopsy Endpoints



- Weight loss ≥5% achieved by diet and exercise occurred in about 22% of patients on resmetirom (12% of placebo patients)
- In resmetirom 100mg arm, ≥5% weight loss was associated with increased fibrosis improvement (41%) and NASH resolution (57%) on liver biopsy; similar improvements in 80 mg arm
- Resmetirom maintained the favorable difference on NASH and fibrosis endpoints from placebos with all weight changes (no weight change, ≥5% weight loss or ≥5% weight gain)

Weight Loss/Resmetirom Impact on Biopsy Endpoints





- Weight loss ≥5% achieved by diet and exercise was observed in about 22% of patients on resmetirom (12% of placebos)
- In resmetirom arm, increased the percentage of patients with fibrosis improvement (41%) and NASH resolution (57%) on liver biopsy
- Resmetirom maintained the favorable difference on NASH and fibrosis endpoints from placebos with all weight changes (no weight change, >=5% weight loss or >=5% weight gain)