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Resmetirom effects on NASH with liver fibrosis in patients with NASH genetic risk alleles

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Disclosure

- Dr. Chalasani serves as a consultant to Madrigal Pharmaceuticals, Inc. He has paid consulting agreements with Zydus, Altimmune, Akero, Pfizer, Merck, BioMe Infusion, and GSK. He receives research support from Exact Sciences and Boehringer-Ingelheim. He has equity in Heligenics, a drug discovery start-up company and Avant Sante, a Contract Research Organization.
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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 NASH and fibrosis
- 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily
- Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage reduction in fibrosis with no worsening of NAS (FI)
- In this analysis, we examined the impact of *PNPLA3*, *HSD17B13*, *TM6SF2, SERPIN (AAT)* and *MBOAT7* genotypes on baseline characteristics and the response to resmetirom on serial liver biopsy, *MRI-PDFF, and biomarkers*

FI, fibrosis improvement; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NASH, nonalcoholic steatohepatitis; NR, NASH resolution.

Methods

KEY ELIGIBILITY CRITERIA

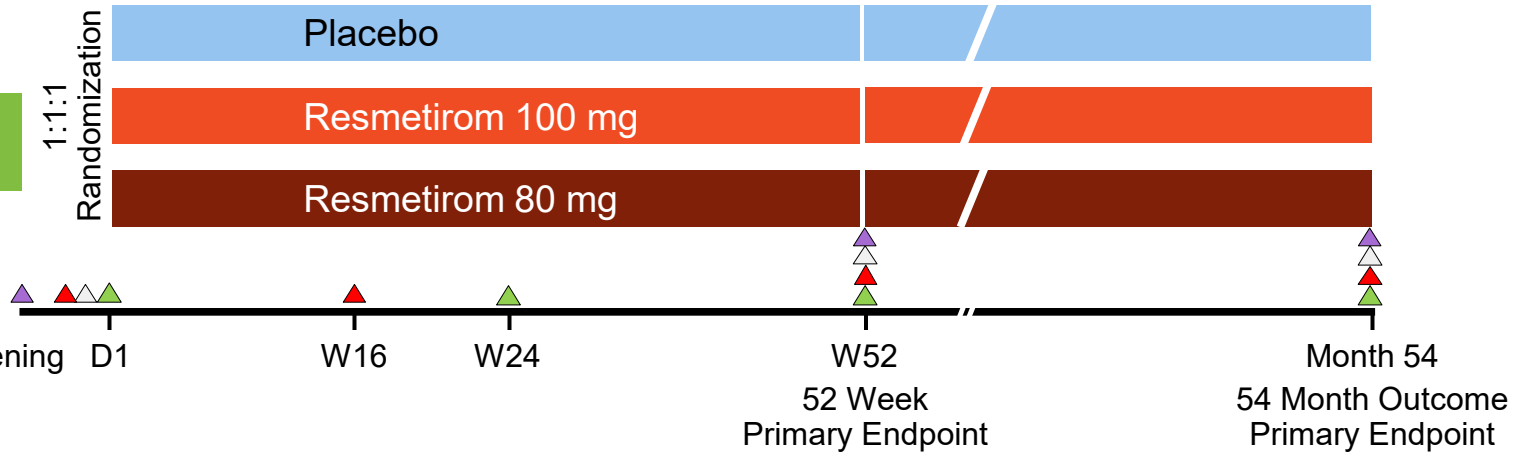
Presence of ≥3 metabolic risk factors

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

Fibrosis stage F1B, F2, or F3

≥8% hepatic fat by MRI-PDFF

MAESTRO-NASH



- *SNPs in PNPLA3 rs738409, HSD17B13 (Hydroxysteroid 17-beta Dehydrogenase 13) rs72613567, TM6SF2 rs58542926, MBOAT7 rs6141738, and SERPINA1 (Alpha-1 Antitrypsin): Variants: Z allele (Glu342Lys) and S allele (Glu264Val)* were genotyped in patients consenting to DNA collection and genetic testing for the response to resmetirom on serial liver biopsy and MRI-PDFF
- Baseline characteristics according to genetic risk markers were assessed
- Biopsy, MRI-PDFF, and other biomarkers responses were analyzed within each treatment arm, comparing wild type, heterozygote and homozygote for each genetic risk allele

CAP, controlled attenuation parameter; LDL-C, low-density lipoprotein cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; VCTE, vibration-controlled transient elastography. Reference: Harrison SA, et al. *N Engl J Med*. 2024;390(6):497-509.

Baseline Characteristics

- Across three treatment arms, 740 patients had genotyping and serial liver biopsy data
- The minor allele general population frequency is shown

Gene	Wildtype	Minor Allele Frequency*	Heterozygous	Homozygous
PNPLA3 rs738409	CC	20-46%	CG	GG
TM6SF2 rs58542926	CC	4-8%	CT	TT
MBOAT7 rs641738	CC	20-43%	CT	TT
SERPINA1 Z allele (Glu342Lys)	MM	1-2%	MZ	ZZ
HSD17B13 rs72613567	TT	15-33%	TA/T	TA/TA

*Range in normal population** also tested for S allele

Allele Frequency in MAESTRO-NASH

- Patient population who consented to genetics and had a Week 52 liver biopsy

	Gene	Wildtype	Heterozygous	Homozygous
PNPLA3	Non-NASH Population	38%	45%	10.5%
	MAESTRO-NASH	31.3%	46.2%	**22.5%**
HSD17B13	Non-NASH Population	52-58*%	37*-40%	6*-8.5%
	MAESTRO-NASH	**65%**	29%	6%
TM6SF2	Non-NASH Population	79-82%	15-21%	0-3%
	MAESTRO-NASH	80%	CT/TT 20%	
MBOAT7	Non-NASH Population	28-29%	47-50%	21-24%
	MAESTRO-NASH	No effect		
SERPINA1 (AAT)	Non-NASH Population	90-95%	9-10%	1-2%
	MAESTRO-NASH	No effect		

**PNPLA3* Caucasian (Hispanic, 25%); *TM6SF2* Europeans TT, 26%; Hispanic 10%

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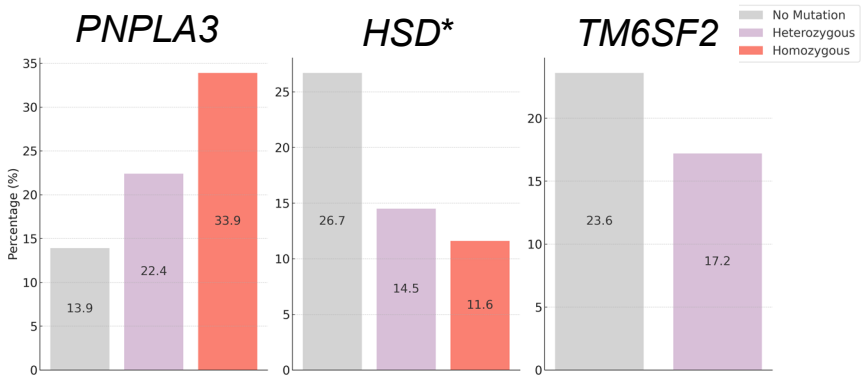
PNPLA3 Baseline Characteristics

Characteristic	No Mutation (N=230)	Heterozygous (N=339)	Homozygous (N=165)
Age at Informed Consent (years) – Mean (SD)	57.3 (9.7)	56.5 (10.9)	55.3 (11.5)
Sex, Male – n (%)	104 (45.2)	156 (46.0)	63 (38.2)
Race, White – n (%)	205 (89.1)	306 (90.3)	141 (85.5)
Ethnicity, Hispanic or Latino – n (%)	32 (13.9)	76 (22.4)	56 (33.9)
Body Mass Index (kg/m^2) – Mean (SD)	35.8 (6.6)	35.7 (6.7)	35.1 (6.5)
Type 2 Diabetes – n (%)	169 (73.5)	222 (65.5)	99 (60.0)
Hypertension – n (%)	193 (83.9)	273 (80.5)	116 (70.3)
Dyslipidemia – n (%)	175 (76.1)	239 (70.5)	105 (63.6)
Hypothyroidism – n (%)	25 (10.9)	54 (15.9)	18 (10.9)
FibroScan VCTE (kPa) at Screening – Mean (SD)	13.9 (8.1)	13.1 (6.0)	12.9 (6.1)
Median (Min, Max)	11.9(4.0, 75.0)	11.6(5.2, 66.4)	11.1(5.2, 45.6)
FibroScan CAP (dB/m) Score at Screening – Mean (SD)	353.5 (39.8)	350.1 (36.0)	334.7 (40.8)
Hepatic Fat Fraction (%) by MRI-PDFF at Screening – Mean (SD)	17.6 (6.7)	18.2 (6.8)	17.5 (6.7)
Median (Min, Max)	16.9 (2.5, 35.1)	17.1 (2.8, 35.3)	16.3 (5.1, 33.8)
Stiffness by MRE (kPa) at Screening – Mean (SD)	3.6 (1.0)	3.5 (1.0)	3.5 (0.98)
Median (Min, Max)	3.5 (1.8, 9.9)	3.3 (1.9, 9.2)	3.4 (2.1, 6.7)
Enhanced Liver Fibrosis Score – Mean (SD)	9.7 (0.83)	9.7 (0.82)	9.9 (0.97)
On GLP-1 Therapy	39 (17.0)	48 (14.2)	26 (15.8)
On Statin Therapy	122 (53.0)	167 (49.3)	61 (37.0)
Baseline Liver Biopsy – n (%)			
NAS ≥5	189 (82.2)	287 (84.7)	139 (84.2)
Fibrosis 1B	19 (8.3)	13 (3.8)	8 (4.8)
Fibrosis 2	72 (31.3)	119 (35.1)	45 (27.3)
Fibrosis 3	137 (59.6)	202 (59.6)	**110 (66.7)**

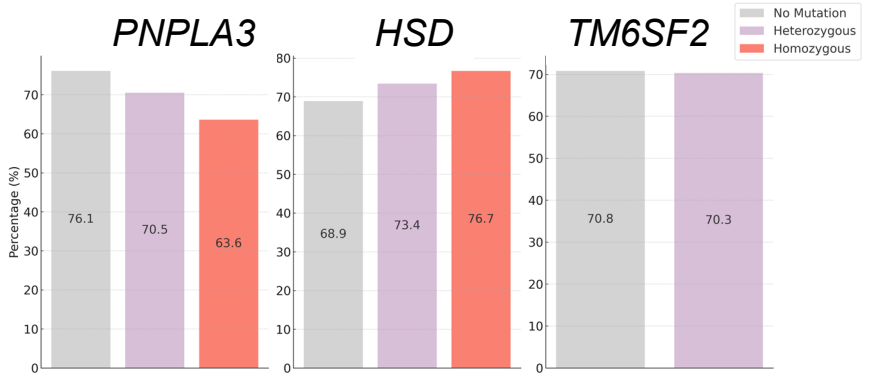
- Focus was on the 3 genetic markers with the most MASH impact: *PNPLA3*, *HSD*, and *TM6SF2*
- A large array of baseline features in the MAESTRO-NASH population were not impacted based on the *PNPLA3* genetic background
- A few features showed differences (highlighted in green)

Baseline Features in NASH Genetic Populations

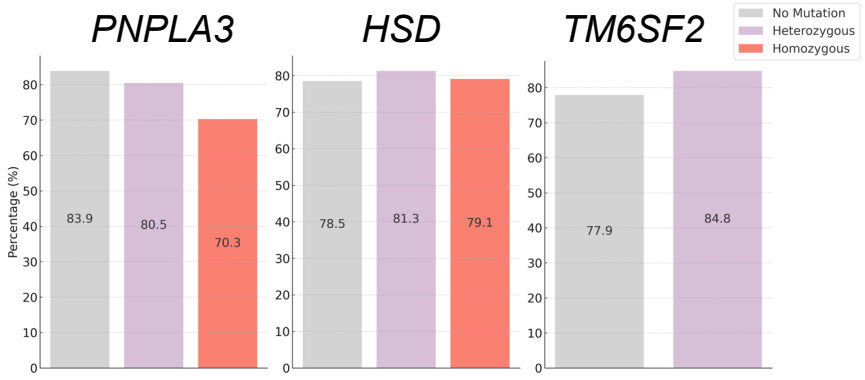
Hispanic



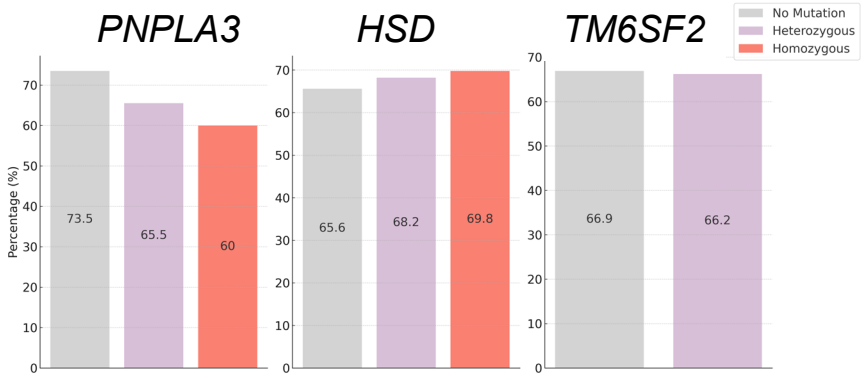
Dyslipidemia



Hypertension



Type 2 diabetes



* Wild type is the risk allele for *HSD*

No mutation
Heterozygote
Homozygote

- Differences in baseline characteristics were explored for patients with and without risk alleles for *PNPLA3*, *HSD17B13* and *TM6SF2*
- Increased Hispanic population in *PNPLA3* and *HSD* risk populations; lower Hispanic in *TM6SF2*
- In the MAESTRO-NASH population, patients with higher genetic risk had lower metabolic risk factors

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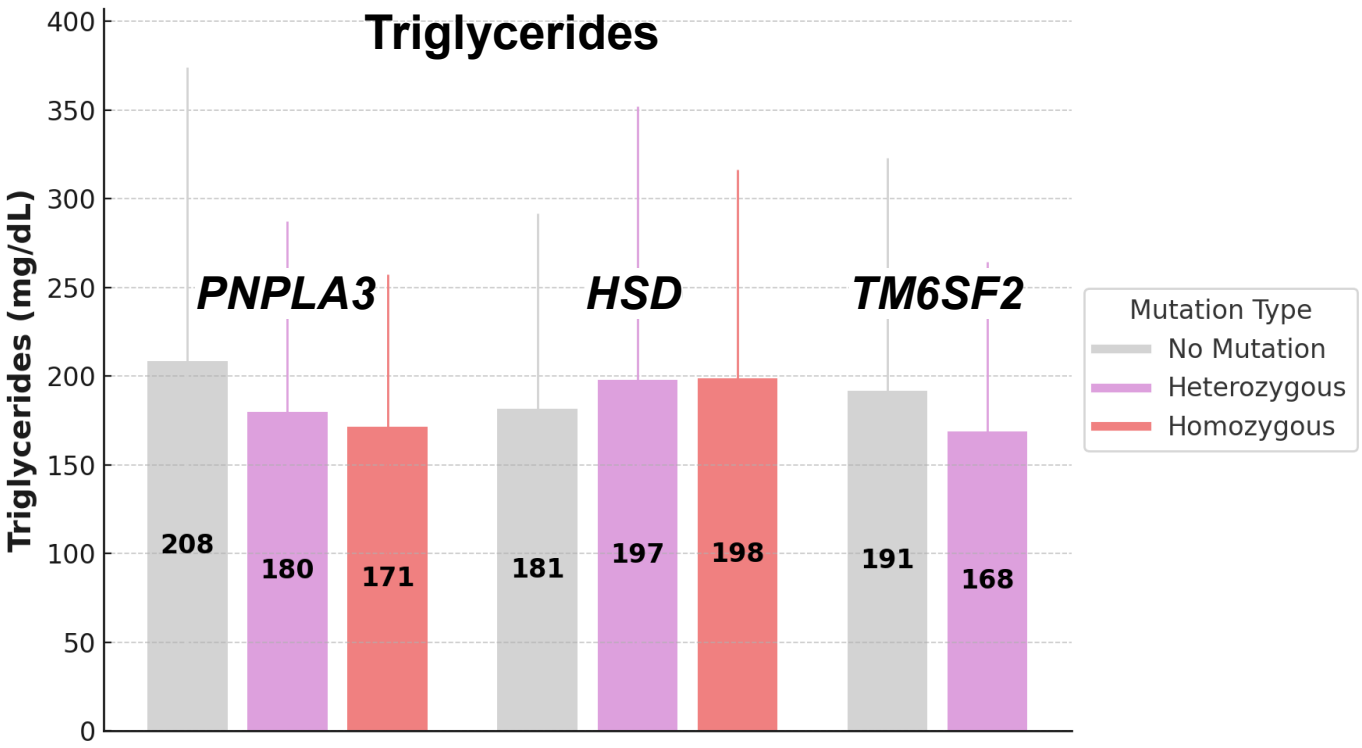
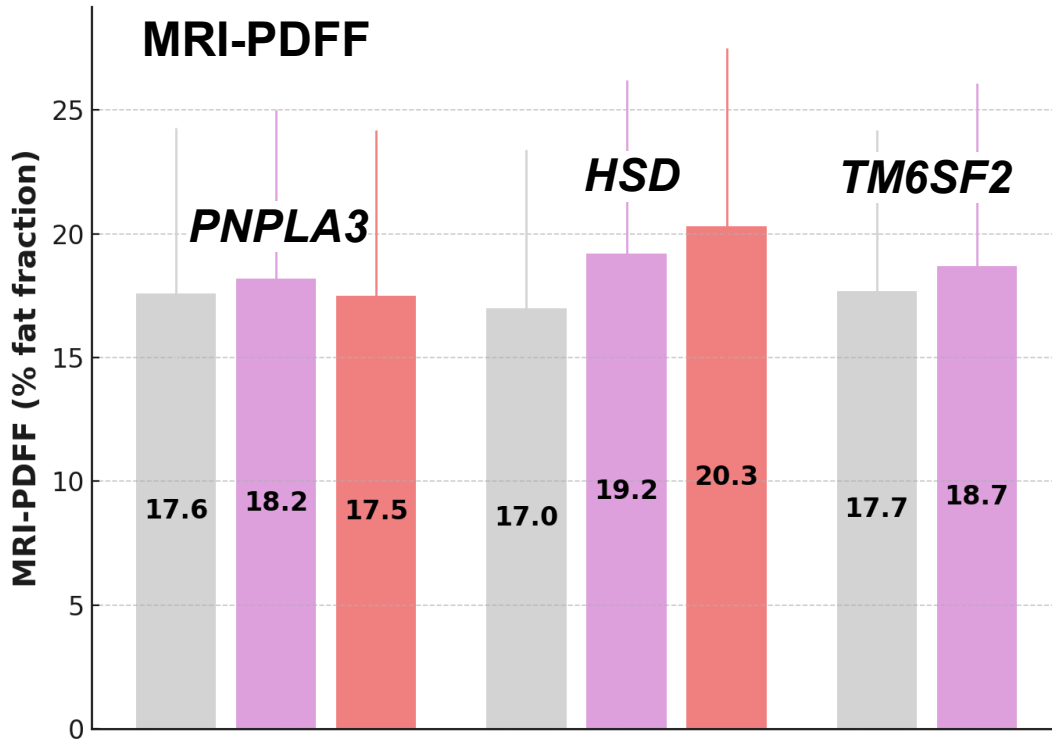
Baseline Triglycerides and MRI-PDFF





- Decreased plasma triglycerides and no change in MRI-PDFF (liver triglycerides) in the *PNPLA3* genetic risk population
- Reduced plasma triglycerides and MRI-PDFF in the *HSD* genetic risk population
- Reduced plasma triglycerides and slight increase in liver triglycerides with *TM6SF2* genetic markers

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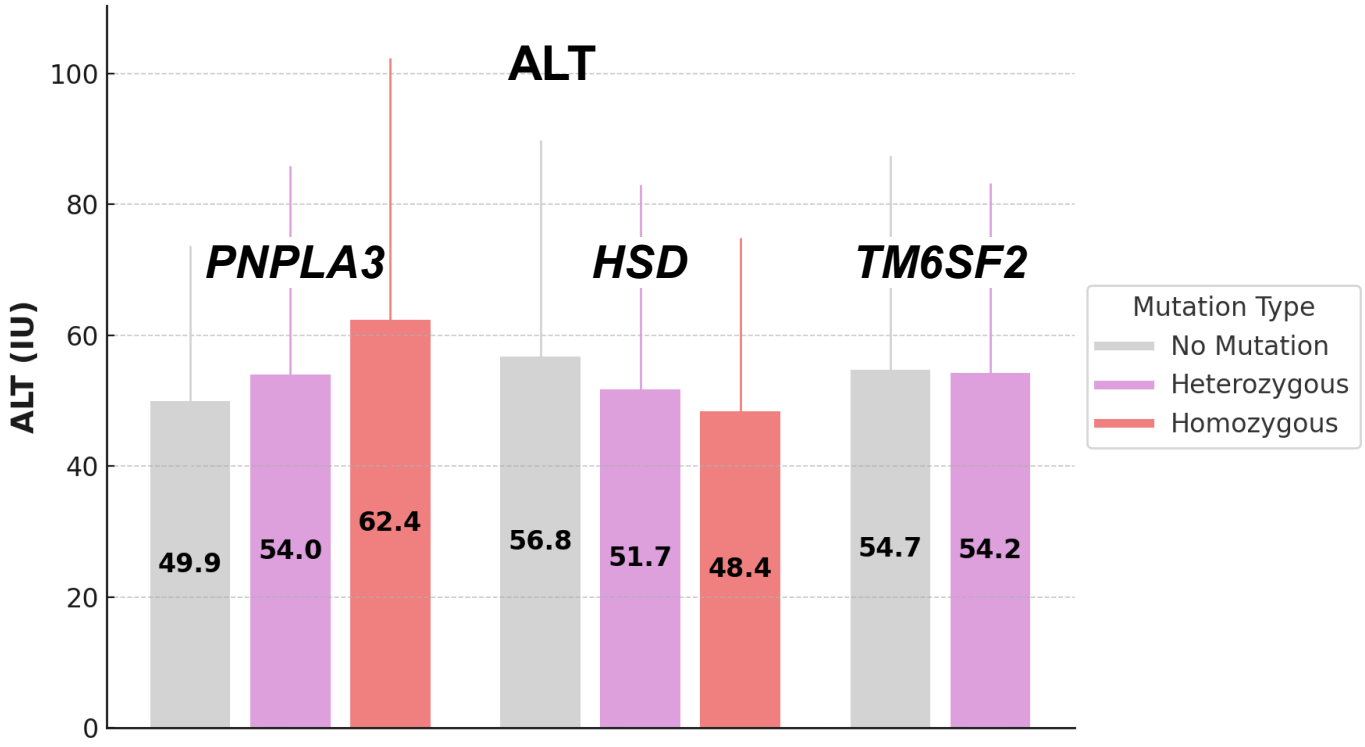
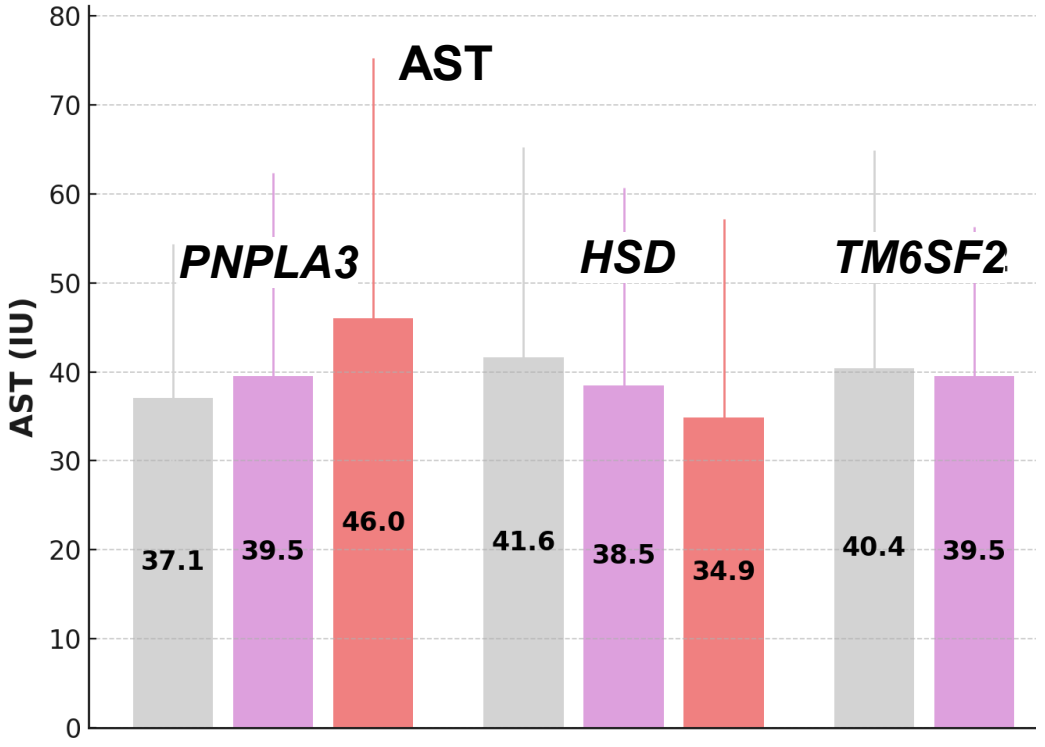
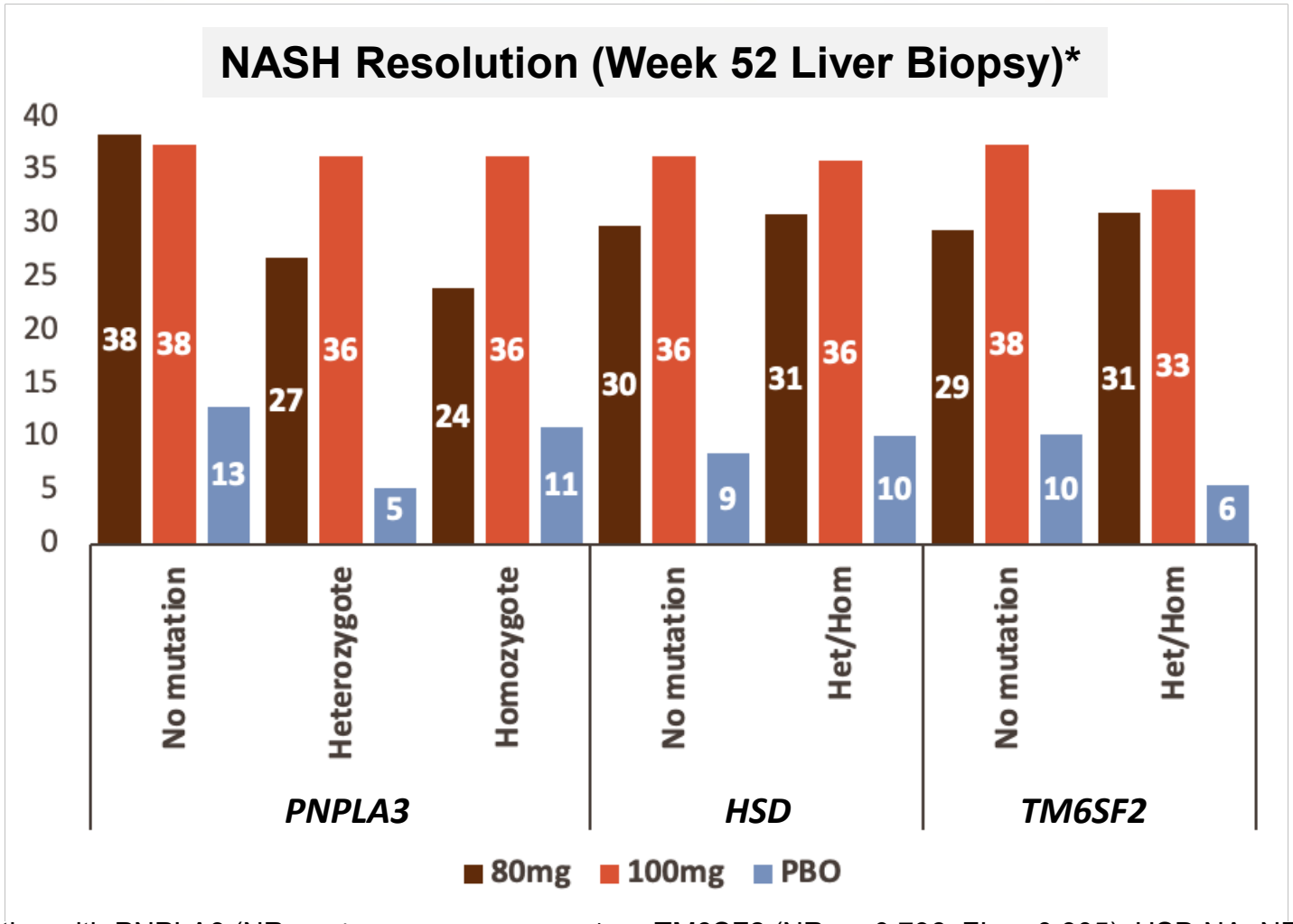
NASH Genetic Background Impact on Baseline Liver Enzymes





- Increased liver enzymes at baseline in patients with genetic risk alleles for PNPLA3 and HSD relative to patients without genetic risk

Impact of NASH Genetic Background on NASH Resolution

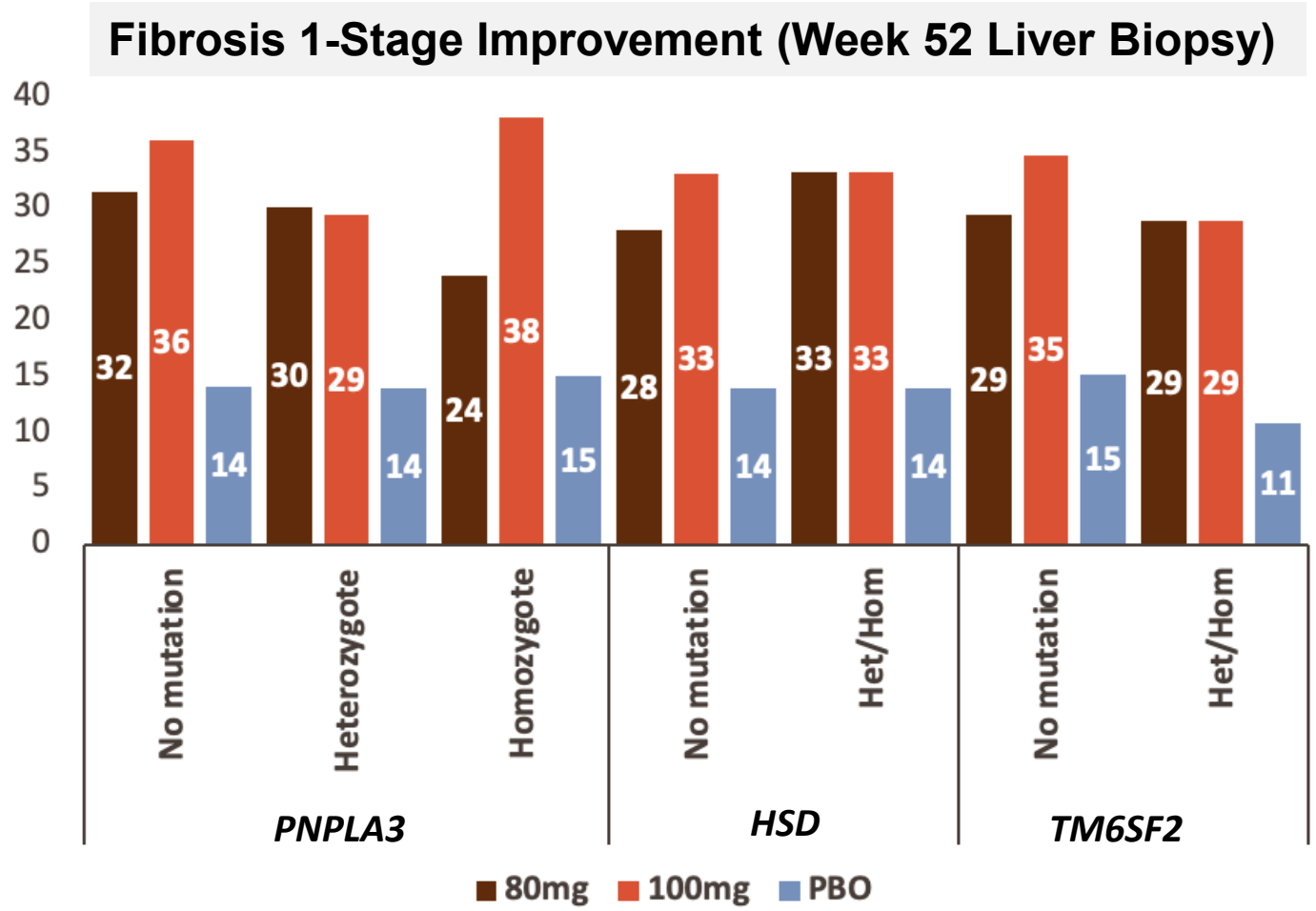


Number of pts	No mutation	Heterozygous	Homozygous
PNPLA3	230	339	165
HSD	483	214	43
TM6SF2	589	145	

- For *HSD* and *TM6SF2* heterozygous and homozygous were combined due to low numbers of patients
- In resmetirom-treated patients, the percentage with NASH resolution was not impacted by any NASH genetic risk markers
- No apparent impact of genetic risk markers on NASH resolution in placebo population

*No interaction with PNPLA3 (NR p-value-0.355, FI, p=0.751); or TM6SF2 (NR, p=0.796, FI, p=0.905); HSD NA; NR, NASH resolution; FI Fibrosis improvement

Impact of NASH Genetic Background on Biopsy Fibrosis Improvement



- In resmetirom-treated patients, the percentage with one stage fibrosis improvement on liver biopsy was not impacted by any NASH genetic risk markers
- No apparent impact of genetic risk markers on fibrosis improvement in the placebo population

*No interaction with PNPLA3 (NR p-value-0.355, FI, p=0.751); or TM6SF2 (NR, p=0.796, FI, p=0.905); HSD NA; NR, NASH resolution; FI Fibrosis improvement

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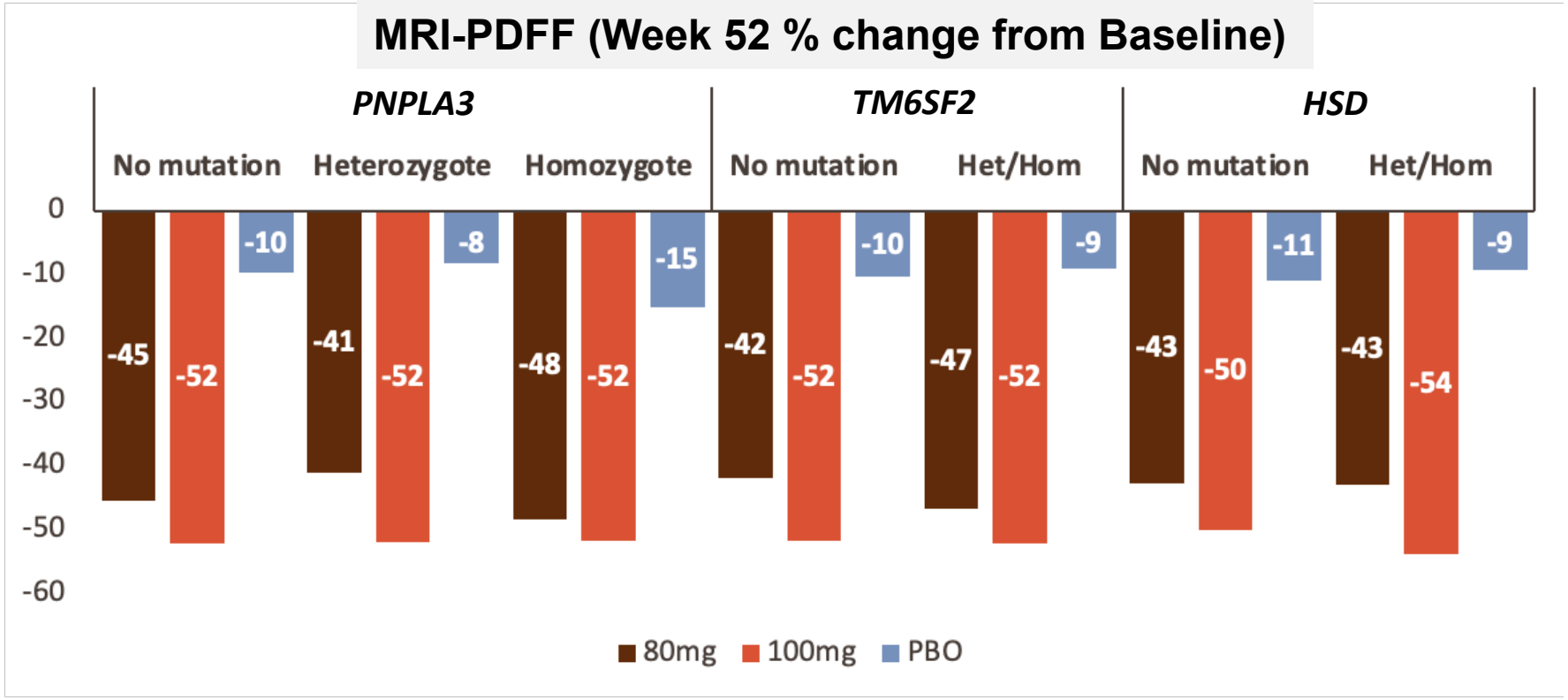
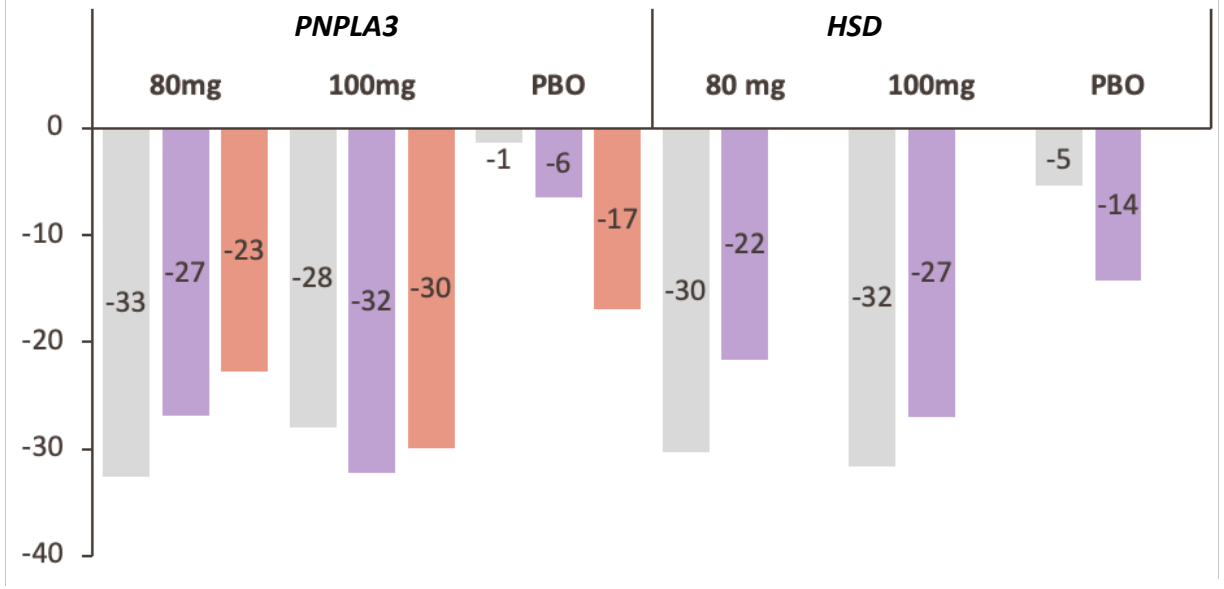
Impact of NASH Genetic Risk Alleles on Liver Fat Reduction



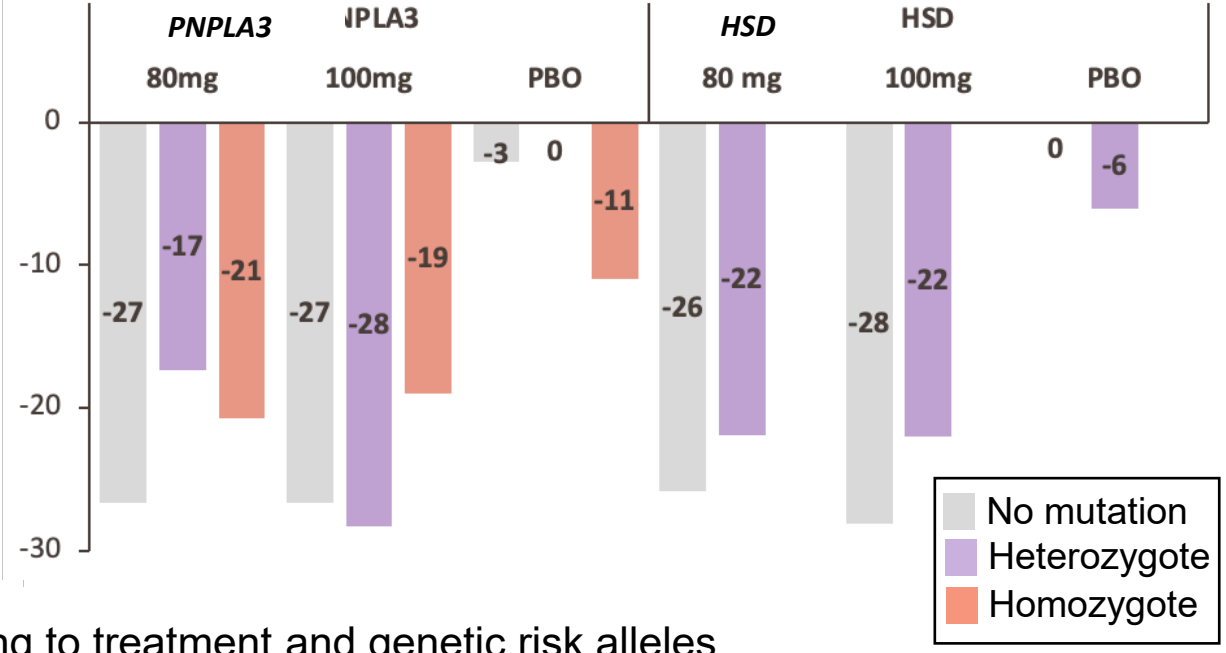
- In resmetirom-treated patients, the relative percentage reduction in PDFF was not impacted by any NASH genetic risk markers
- No apparent impact of genetic risk markers on MRI-PDFF reduction in the placebo population

Liver Enzyme Responses

ALT (Week 48, % change from baseline)

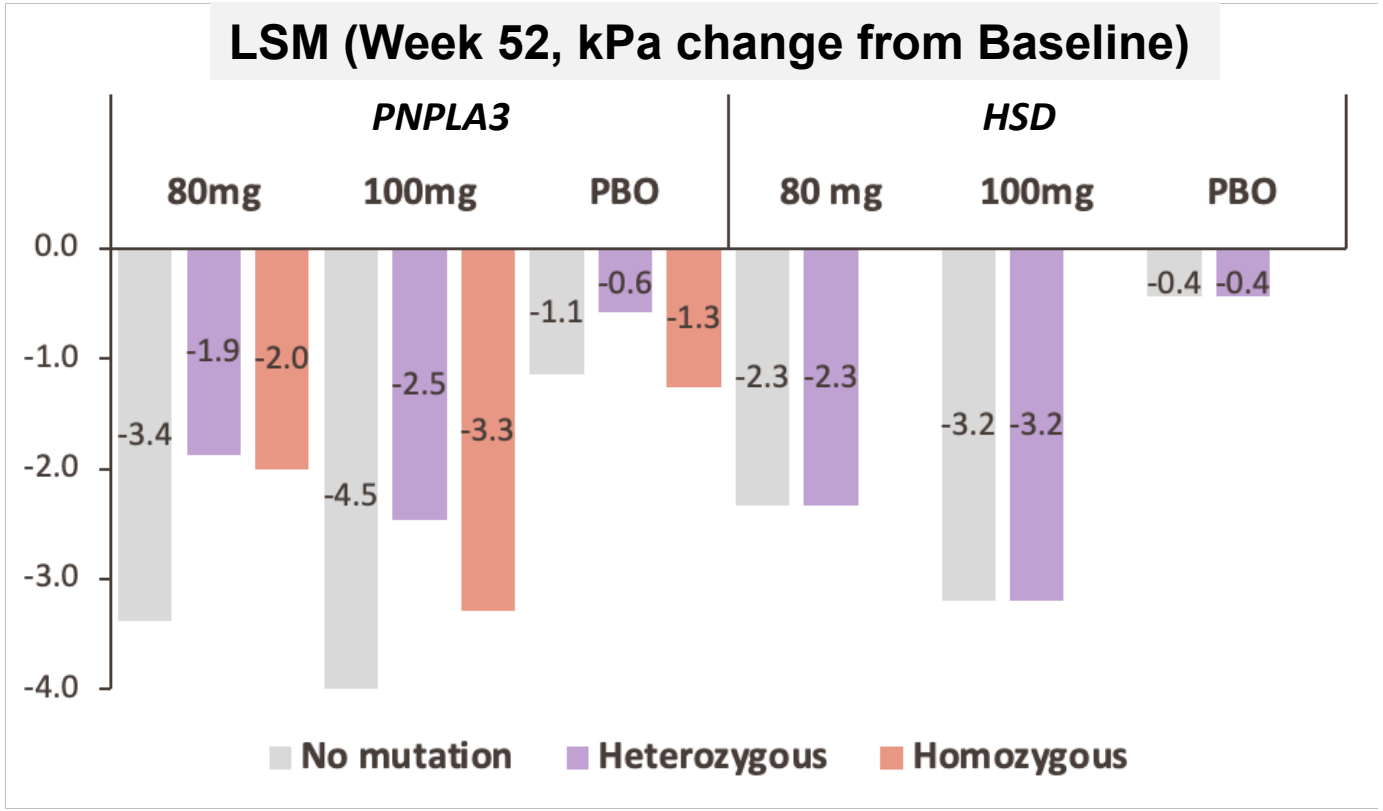


AST (Week 48, % change from baseline)



- Liver enzyme responses were evaluated according to treatment and genetic risk alleles
- Increased liver enzymes at baseline in patients with genetic risk markers for *PNPLA3* and *HSD* relative to patients without genetic risk
- Lowering of ALT and AST at Week 48 by resmetirom was robust and independent of genetic risk

VCTE Response



- Baseline FibroScan VCTE (LSM) was not different in F2/F3 NASH patients with genetic risk markers *PNPLA3* and *HSD* compared with patients without genetic risk markers
- Resmetirom compared with placebo lowered LSM at 52 Weeks independent of risk alleles

LSM, liver stiffness measurement

Summary

- A significant fraction of patients enrolled in MAESTRO-NASH had genetic risk markers, particularly *PNPLA3*, *HSD17*, and *TM6SF2* that impacted several baseline features including ethnicity, metabolic features, baseline liver enzyme levels and lipids
- Higher genetic risk was associated with fewer metabolic risk factors in MAESTRO-NASH's noncirrhotic NASH population suggesting that patients with high genetic risk require less metabolic risk to progress to an equivalent NASH fibrosis stage as patients without genetic risk factors
- In the MAESTRO-NASH study the presence of NASH risk alleles did not influence the treatment response to resmetirom on liver biopsy, imaging or other markers of response