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Emerging Directions in the Management of NASH

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This program is supported by an educational grant from Gilead Sciences, Inc.

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Stephen A. Harrison, MD, COL (Ret.), FAASLD, has disclosed that he has received consulting fees from Axcella, Capulus, the Chronic Liver Disease Foundation, Cirius, Genfit, Echosens, Histoindex, Intercept, Madrigal, NGM Bio, Novartis, Novo Nordisk, Perspectum, and Prometheus; has received fees for non-CME/CE services from AbbVie, Alexion, and Gilead Sciences; and has an ownership interest in Cirius and Madrigal.

Phase III/IIb Studies

Emerging Treatments in NASH: Phase III

Drug	Mechanism of Action	Study Population	Trial	Primary Endpoint
Elafibranor	PPAR α/δ agonist	▪ NASH with fibrosis (stage 1-3)	▪ RESOLVE-IT[1]	NASH resolution without fibrosis worsening; long-term composite of all-cause mortality, cirrhosis, and liver-related outcomes
Obeticholic acid	FXR agonist	▪ NASH with fibrosis (stage 1-3)	▪ REGENERATE[2]	Fibrosis improvement without NASH worsening; NASH resolution without fibrosis worsening; all-cause mortality and liver-related outcomes
Selonsertib	ASK1 inhibitor	▪ NASH with fibrosis (stage 3) ▪ NASH with compensated cirrhosis	▪ STELLAR 3[3] ▪ STELLAR 4[4]	Fibrosis improvement without NASH worsening, EFS
Cenicriviroc	CCR2/5 antagonist	▪ NASH with fibrosis (stage 2/3)	▪ AURORA[5]	Fibrosis improvement without NASH worsening; composite of progression to cirrhosis, liver-related outcomes, and all-cause mortality

References in slidenotes.

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Emerging Treatments in NASH: Phase IIb

Drug	Mechanism of Action	Study Population	Trial	Primary Endpoint
Aramchol	Synthetic fatty acid/bile acid conjugate	NASH	Aramchol_005[1]	Percent change in liver triglycerides
Emricasan	Pan-caspase inhibitor	NASH with fibrosis (stage 1-3)	ENCORE-NF[2]	Fibrosis improvement without NASH worsening

1. ClinicalTrials.gov. NCT02279524. 2. ClinicalTrials.gov. NCT02686762.

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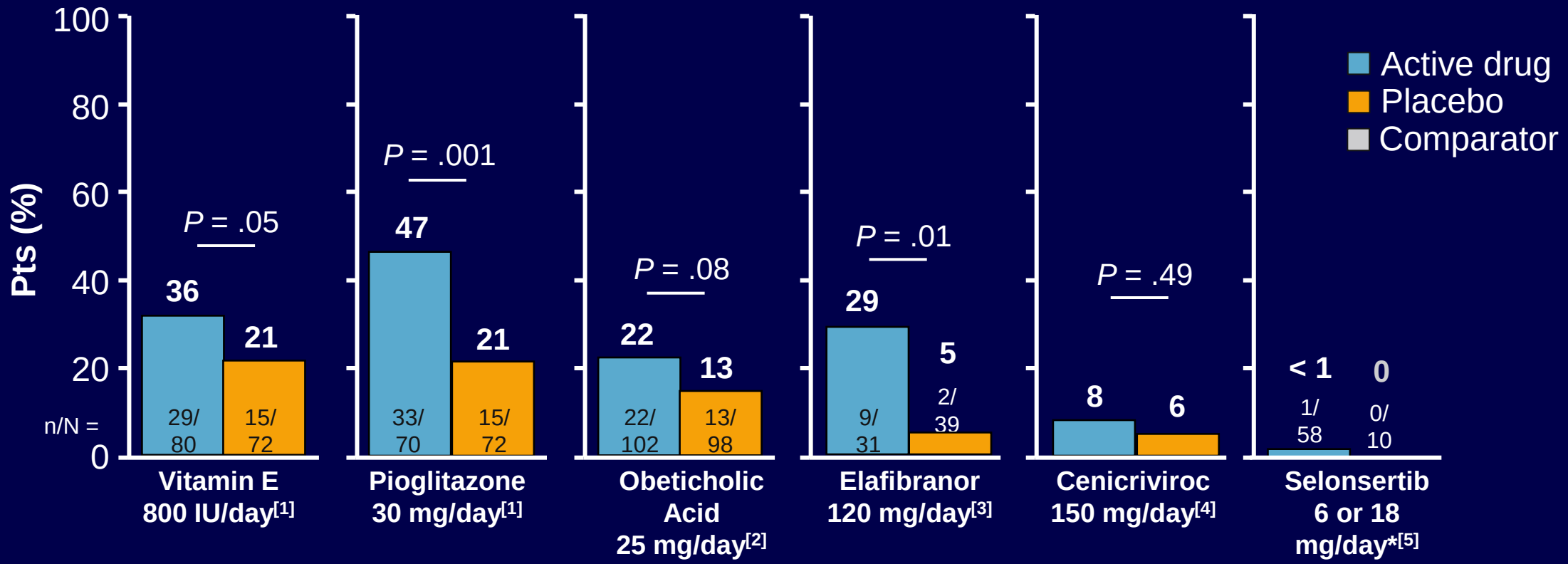
Key NASH Therapies: Resolution of NASH

- Results from separate studies, not head to head, with different endpoint definitions
  - Time points and populations may differ among studies



*Calculated from publication, which reported separate results for each dose. Simtuzumab alone comparator treated as de facto placebo due to lack of efficacy in multiple studies.

References in slidenotes.

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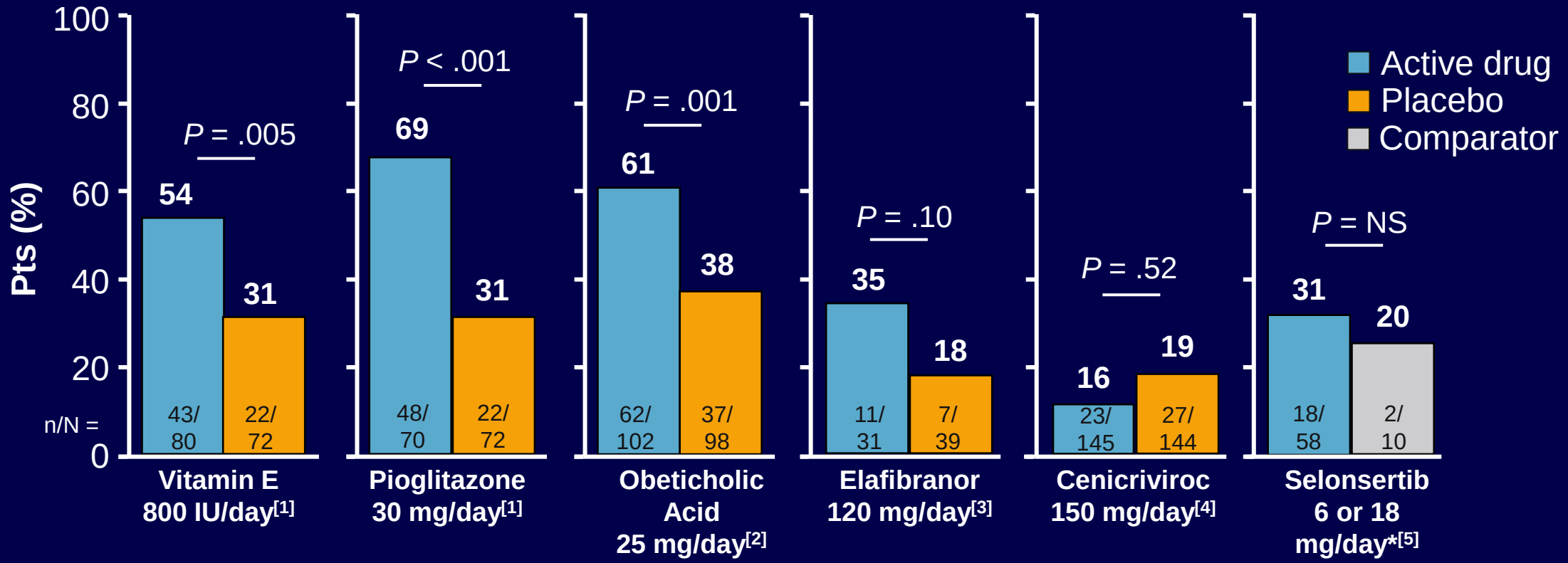
Key NASH Therapies: Improvement in Steatosis

- Results from separate studies, not head to head, with different endpoint definitions
  - Time points and populations may differ among studies



*Calculated from publication, which reported separate results for each dose. Simtuzumab alone comparator treated as de facto placebo due to lack of efficacy in multiple studies.

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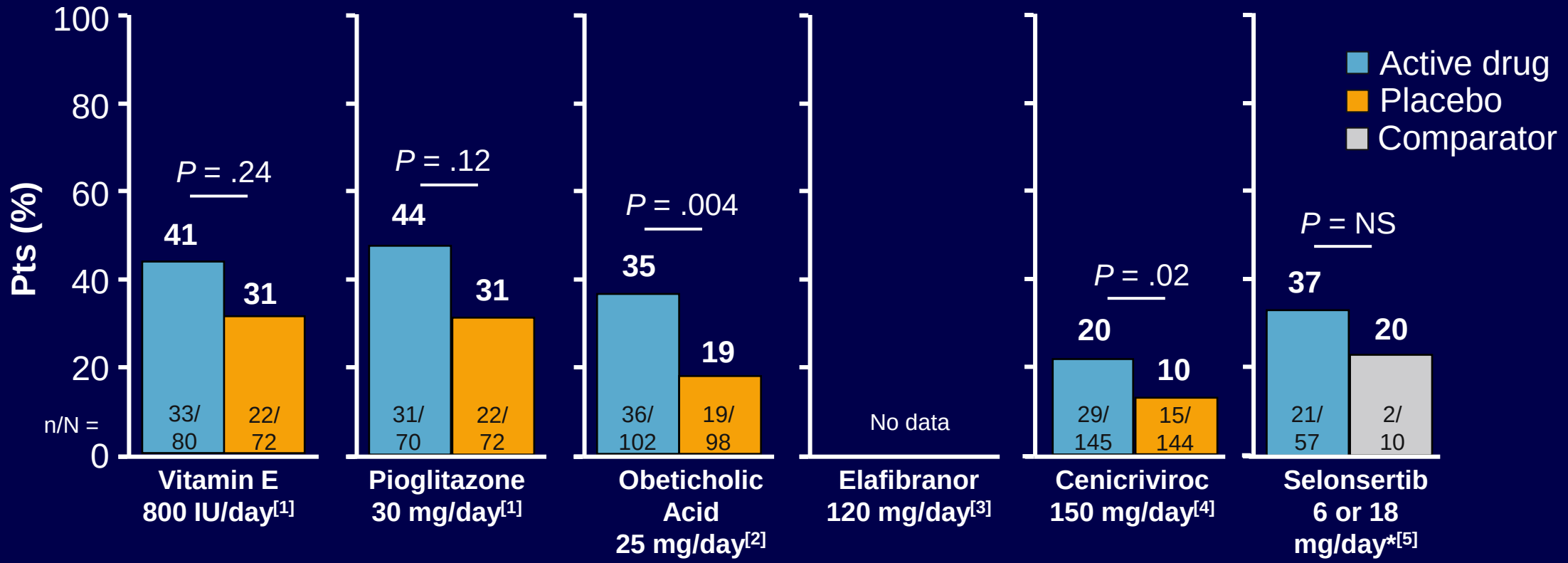
Key NASH Therapies: Improvement in Fibrosis

- Results from separate studies, not head to head
  - Time points and populations may differ among studies



*Calculated from publication, which reported separate results for each dose. Simtuzumab alone comparator treated as de facto placebo due to lack of efficacy in multiple studies.

References in slidenotes.

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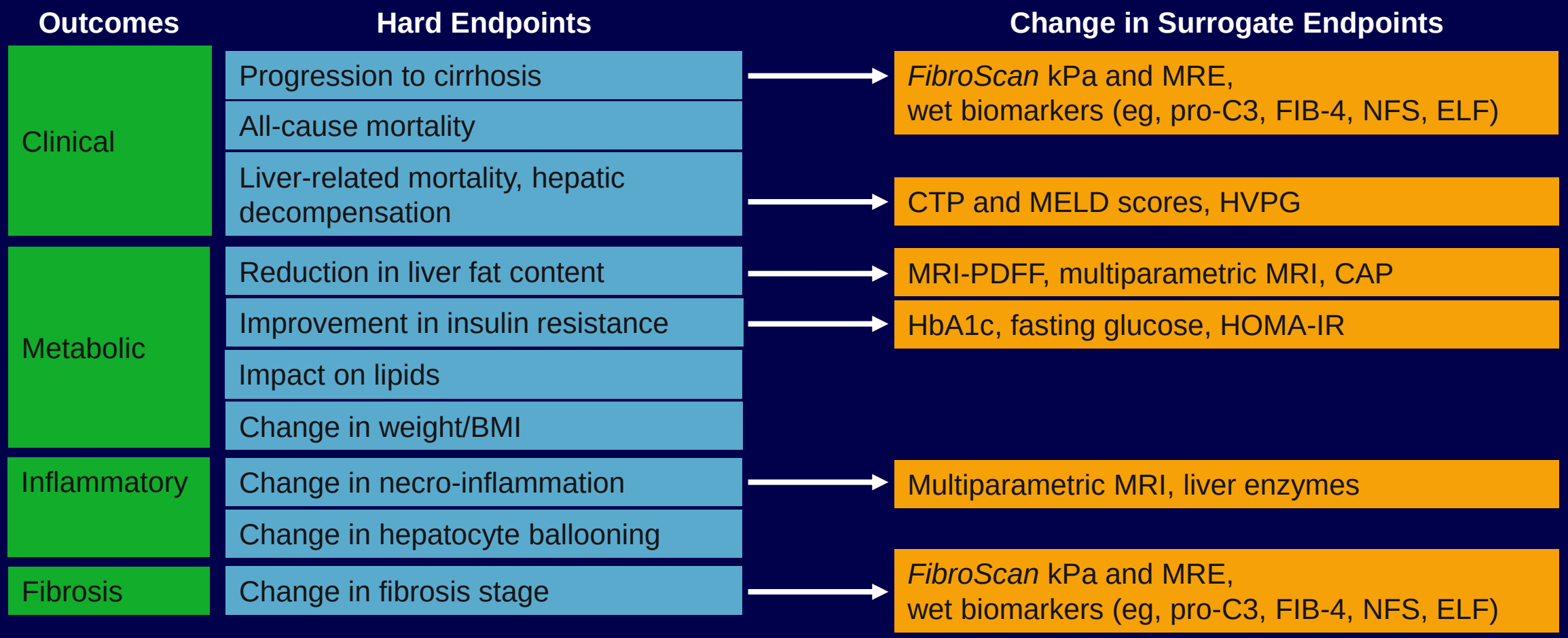
Understanding Endpoints of Newer Studies

Endpoints for Outcome Measures in NASH



Konerman MA, et al. J Hepatol;[In press].

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	Focus	Timeline	Liver Biopsy	Metabolic	Inflammatory	Fibrosis	Clinical
Phase IIa	▪ Proof of concept ▪ Short-term safety ▪ Clarify target engagement	Abbreviated (12-24 wks)	Not required	Δ Hepatic fat via MRI-PDFF or CAP	▪ Δ Liver enzymes and other biomarkers ▪ Multiparametric MRI	▪ Δ Biomarkers ▪ MRE, FS kPa	
Phase IIb	▪ Assess efficacy ▪ Safety and adverse events ▪ Therapeutic dosing	Intermediate (24-72 wks)	Paired	Δ Hepatic fat via histology ± MRI-PDFF/CAP	▪ Δ Inflammation and ballooning (NAS) ▪ Resolution of NASH without worsening of fibrosis ▪ Multiparametric MRI	▪ Δ Fibrosis stage without worsening of NASH ▪ MRE, FS kPa	
Phase III	▪ Confirm efficacy ▪ Longer-term safety and efficacy ▪ Clinical outcomes	Longer term (yrs)	Paired	Δ Hepatic fat via histology ± MRI-PDFF/CAP	▪ Δ Inflammation and ballooning (NAS) ▪ Resolution of NASH without worsening of fibrosis ▪ Multiparametric MRI	▪ Δ Fibrosis stage without worsening of NASH ▪ MRE, FS kPa	▪ Progression to cirrhosis ▪ Hepatic decompensation ▪ Overall mortality ▪ Liver-related mortality ▪ HCC or transplantation
Adaptive	▪ Cover aims of phase II and III trials sequentially	▪ Multiple ▪ Interim analysis to consider dropping study arms and rerandomization	Paired	▪ Δ Hepatic fat via MRI-PDFF or CAP early part of trial ▪ Δ Hepatic fat via histology later part of trial	▪ Δ Liver enzymes and other biomarkers or multiparametric MRI early part of trial ▪ Δ Histology later part of trial	▪ Early: Δ Biomarkers, MRE, FS kPa ▪ Later: Δ histology	▪ Assess clinical outcomes at end of trial

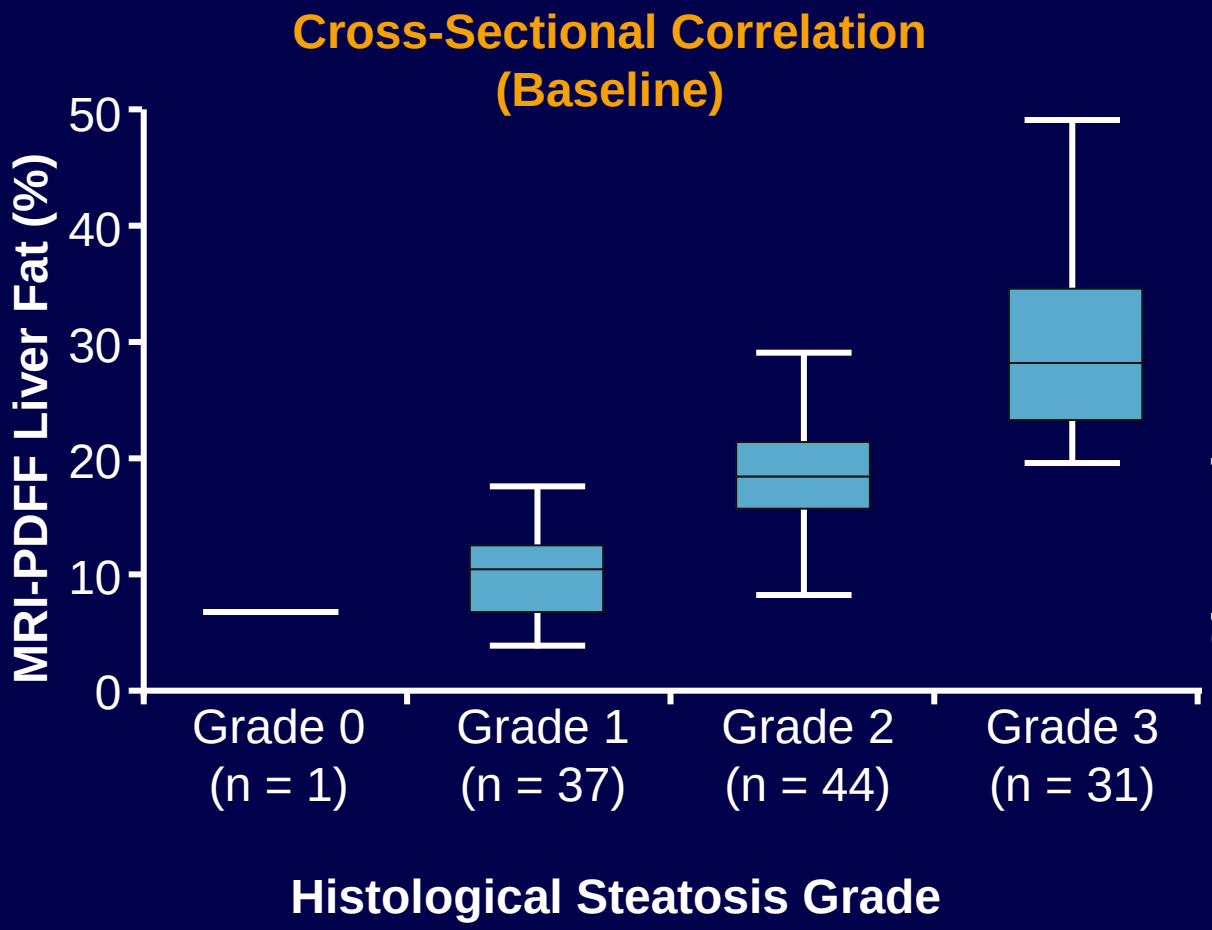
Konerman MA, et al. J Hepatol;[In press].

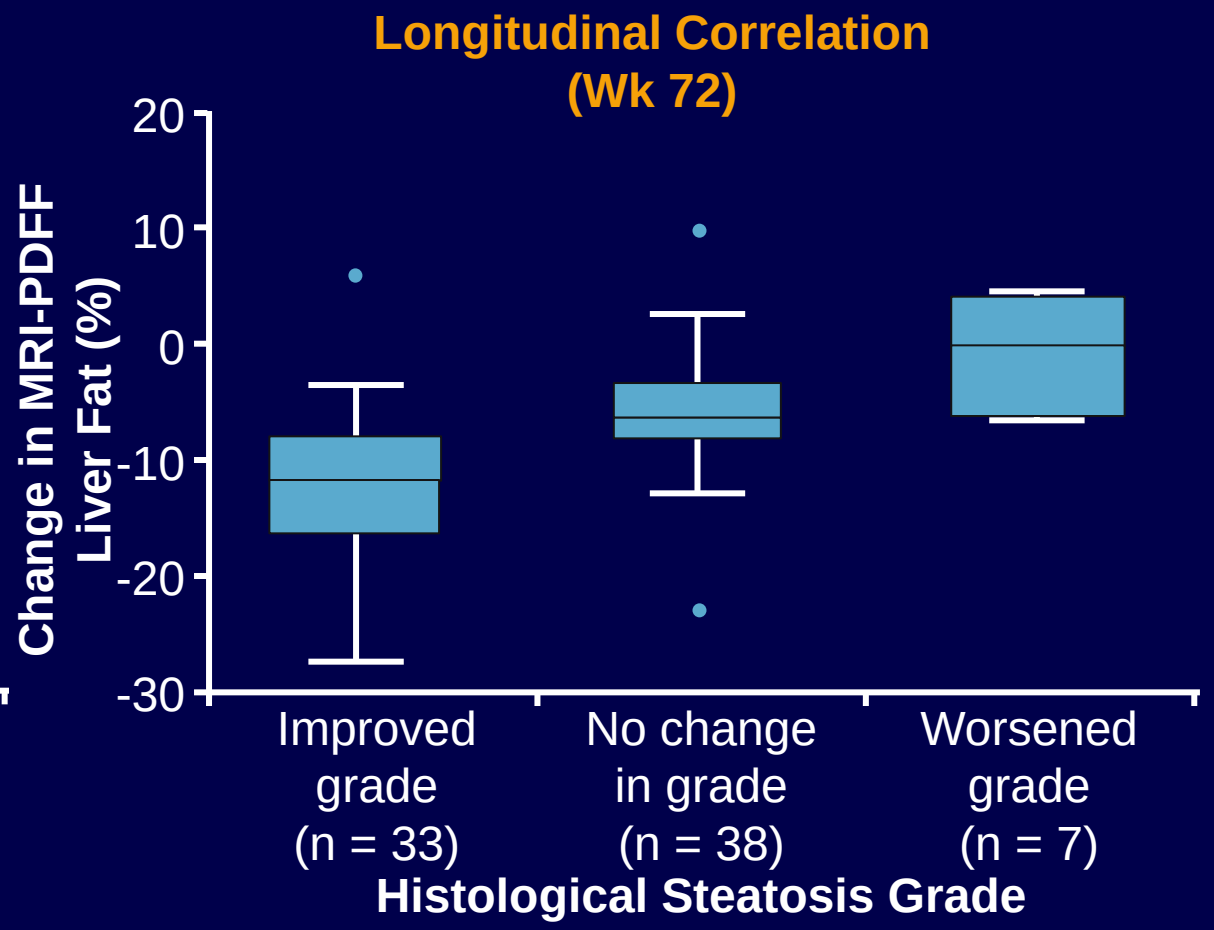
FLINT Cohort: Diagnostic Performance of MRI-PDFF vs Biopsy in NASH

- Prospectively designed study in a multicenter, randomized, double-blind, placebo-controlled trial of obeticholic acid vs placebo for 72 wks in pts with NASH (N = 283)
- MRI-PDFF compared with histological steatosis grade
  - Cross-sectionally: pts with MRI and liver biopsy at BL, n = 113
  - Longitudinally: pts with MRI and liver biopsy at BL, Wk 72, n = 78

Middleton MS, et al. Gastroenterology. 2017;153:753-761.

FLINT Cohort: Correlation of MRI-PDFF With Steatosis Grade at Baseline and After Treatment





Median values given with IQRs, dots are outliers.

Middleton MS, et al. Gastroenterology. 2017;153:753-761.

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Phase IIa Studies in NASH

Emerging Treatments in NASH: Phase II

Drug(s)	Mechanism of Action	Study Population[1]	Trial	Primary Endpoint
LJN452	FXR agonist	NASH (fibrosis stage 0-3), elevated ALT **or** PDFF > 10%, obesity, T2DM	FLIGHT-FXR[2]	Adverse event profile; change in transaminases
LMB763	FXR agonist	NASH (fibrosis stage 0-3), elevated ALT **or** PDFF > 10%, obesity, T2DM	CLMB763X2201[3]	Adverse event profile and safety; change in transaminases
GS-9674	FXR agonist	NASH, MRE > 2.5 kPa, PDFF > 10%	GS-US-402-1852[4]	Safety and tolerability
GS-9674 + GS-0976	FXR agonist + ACC inhibitor	NASH (fibrosis stage 2-3) **or** MRE > 2.88 kPa, PDFF ≥ 10% **or** MRE > 4.67 kPa, not compensated	GS-US-384-3914[5]	Safety and tolerability
GS-0976	ACC inhibitor	NAFLD or NASH without cirrhosis	GS-US-426-3989[6]	Safety and tolerability
PF-05221304	ACC inhibitor	NASH (fibrosis stage 1-3), MRE ≥ 2.5 kPa, PDFF ≥ 8%	C1171002[7]	Dose-response effect on liver fat

References in slidenotes.

Slide credit: clinicaloptions.com

Emerging Treatments in NASH: Phase II

Drug	Mechanism of Action	Study Population[1]	Trial	Primary Endpoint
Saroglitazar	PPAR α/ɣ agonist	NAFLD (fibrosis stage 0-3), ALT > 1.5 ULN	EVIDENCES II[2]	Change in ALT
IVA337	PPAR α/δ/ɣ agonist	NASH, SAF fibrosis score < 4	NATIVE[3]	Improvement of SAF activity score
Liraglutide	GLP-1 analogue	NASH (fibrosis stage 1-4), compensated cirrhosis	LEAN[4,5]	Liver histological improvement
Semaglutide	GLP-1 analogue	NASH (fibrosis stage 2-3)	NN9931-4296[6]	NASH resolution without worsening of fibrosis
JKB-121	TLR-4 antagonist	NASH (fibrosis stage 1-3)	Pro00062677[7]	Safety and tolerability; change in ALT, hepatic fat; TTR
NGM282	FGF19 agonist	NASH (fibrosis stage 1-3)	15-0105[8]	Change in hepatic fat
BMS-986036	Pegylated FGF21	NASH (fibrosis stage 1-3)	MB130-045[9]	Safety and tolerability; change in hepatic fat
MGL-3196	THR-β agonist	NASH (fibrosis stage 1-3)	MGL-3196-05[10]	Change in hepatic fat
Volixibat	ASBT inhibitor	NASH (fibrosis stage 0-3)	SHP626-201[11]	Improvement in NAS without fibrosis worsening

References in slidenotes.

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Emerging Treatments in NASH: Phase II

Drug	Mechanism of Action	Study Population[1]	Trial	Primary Endpoint
MSDC-0602K	mTOT modulator	NASH (fibrosis stage 1-3)	EMMINENCE[2]	Improvement in NAS without fibrosis worsening
LIK066	SGLT1/2 inhibitor	NASH (fibrosis stage 1-3)	CLIK066X2204[3]	Change in ALT
BI 1467335	AOC3 inhibitor	NASH (fibrosis stage 1-3) or MRE ≥ 3.6 4kPa, PDFF ≥ 5%	1386-0004[4]	Target enzyme activity
IMM-124E	Anti-LPS hyperimmune bovine colostrum; induction of regulatory T-cells	NASH (fibrosis stage 0-3)	IMM-124E-2001[5]	Safety and tolerability; change in hepatic fat, ALT

References in slidenotes.

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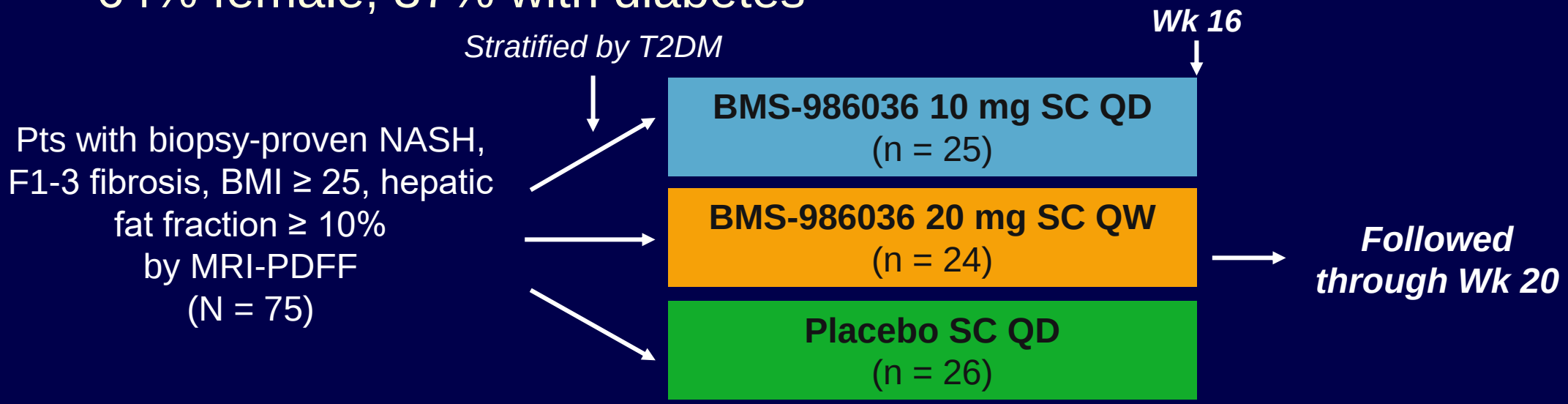
BMS-986036: Pegylated FGF21

BMS-986036 in Pts With NASH, F1-3 Fibrosis

- Multicenter, randomized, double-blind, placebo-controlled phase II study
  - 64% female, 37% with diabetes



Placebo lead-in for all pts 1 wk prior to randomization.
Planned N = 90; enrollment ended early due to significant effect of BMS-986036 on primary endpoint in preplanned interim analysis at Wk 8.

- Primary endpoint: absolute change in hepatic fat fraction

Sanyal A, et al. AASLD 2017. Abstract 182.

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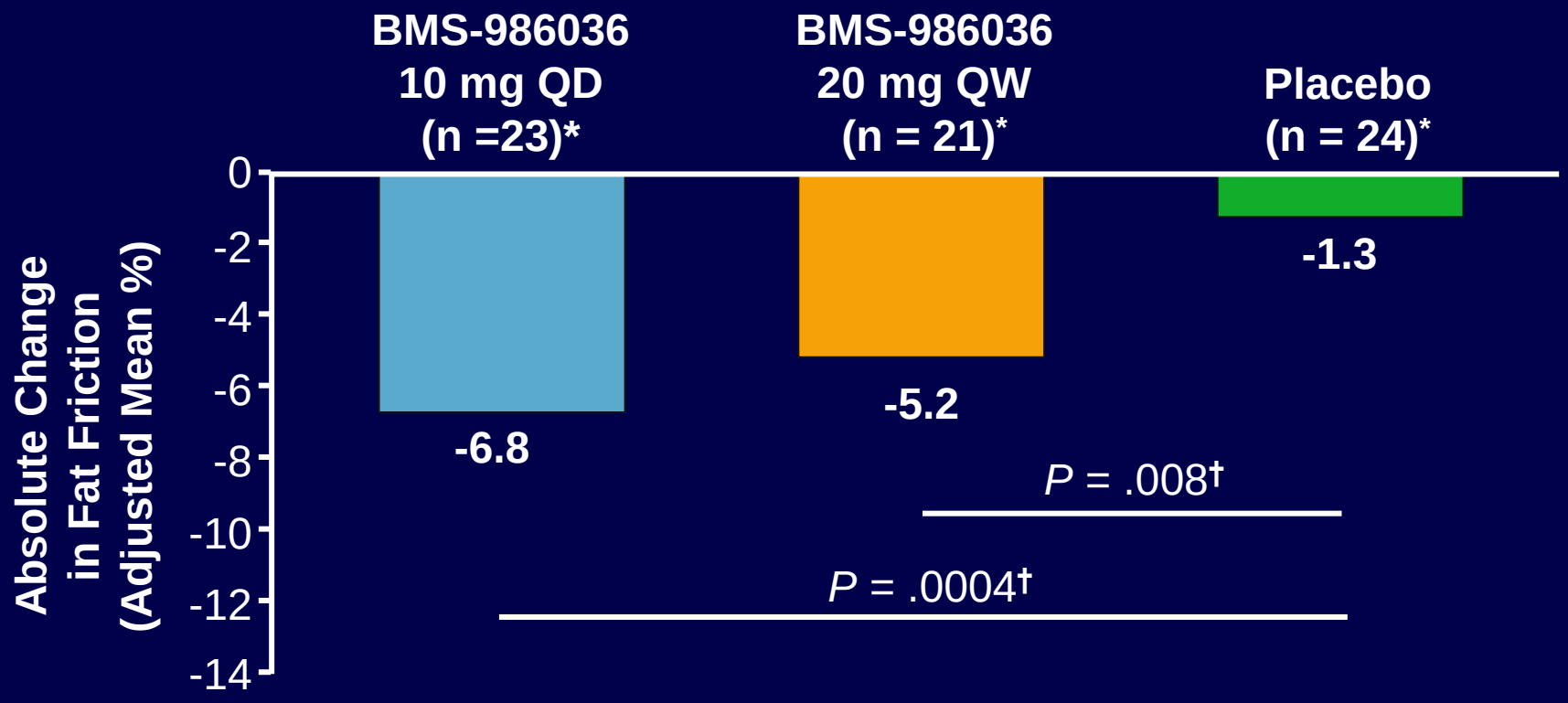
BMS-986036 Primary Endpoint: Absolute Change in Hepatic Fat Fraction at Wk 16

- Significant reduction in liver fat content vs placebo by MRI-PDFF



* In each arm, 1 pt completed treatment but lacked adequate MRI-PDFF scans at BL and Wk 16.
†Inferential statistical analyses by MMRM, not adjusted for multiple comparisons.

Sanyal A, et al. EASL 2017. Abstract LBO-02.

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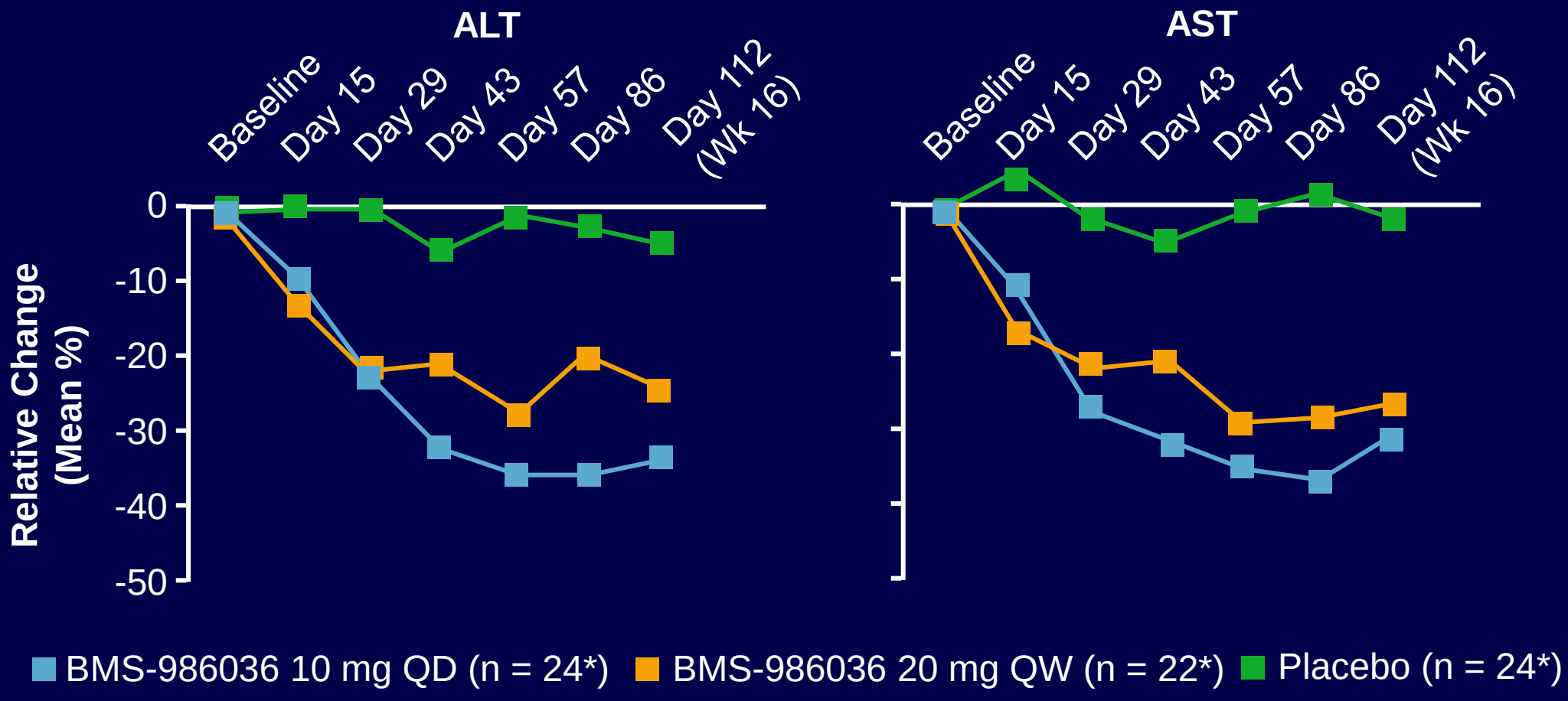
BMS-986036: Relative Change in ALT and AST



*Indicates number of pts with ALT/AST data at end of treatment.

Sanyal A, et al. EASL 2017. Abstract LBO-02.

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BMS-986036: Safety

Safety Event, n (%)	BMS-986036 10 mg QD (n = 25)	BMS-986036 20 mg QW (n = 23)	Placebo (n = 26)
Serious AEs	1 (4)*	0	1 (4)†
AEs occurring in > 10% of pts			
▪ Diarrhea	3 (13)	5 (22)	2 (8)
▪ Nausea	4 (16)	3 (13)	2 (8)
▪ Frequent bowel movements	5 (20)	0	0
Treatment-emergent grade 3/4 laboratory abnormalities	1 (4)	2 (9)	2 (8)

Serious AEs included *depression/suicide attempt and †cellulitis; none considered treatment related.

- No treatment-related serious AEs, discontinuations for AEs, or deaths
- Most AEs mild, none severe

Sanyal A, et al. EASL 2017. Abstract LBO-02.

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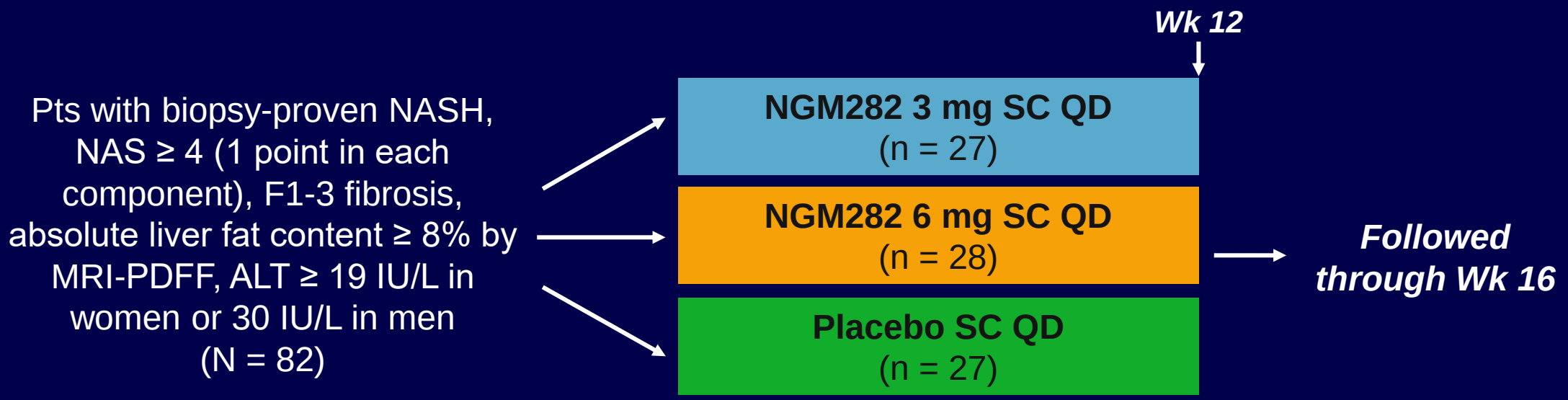
NGM282:
FGF19 Agonist

NGM282 in Pts With NASH, F1-3 Fibrosis

- Multicenter, randomized, double-blind, placebo-controlled phase II study



- Primary endpoint: decrease in absolute liver fat content ≥ 5%

Harrison SA, et al. EASL 2017. Abstract LBO-07.

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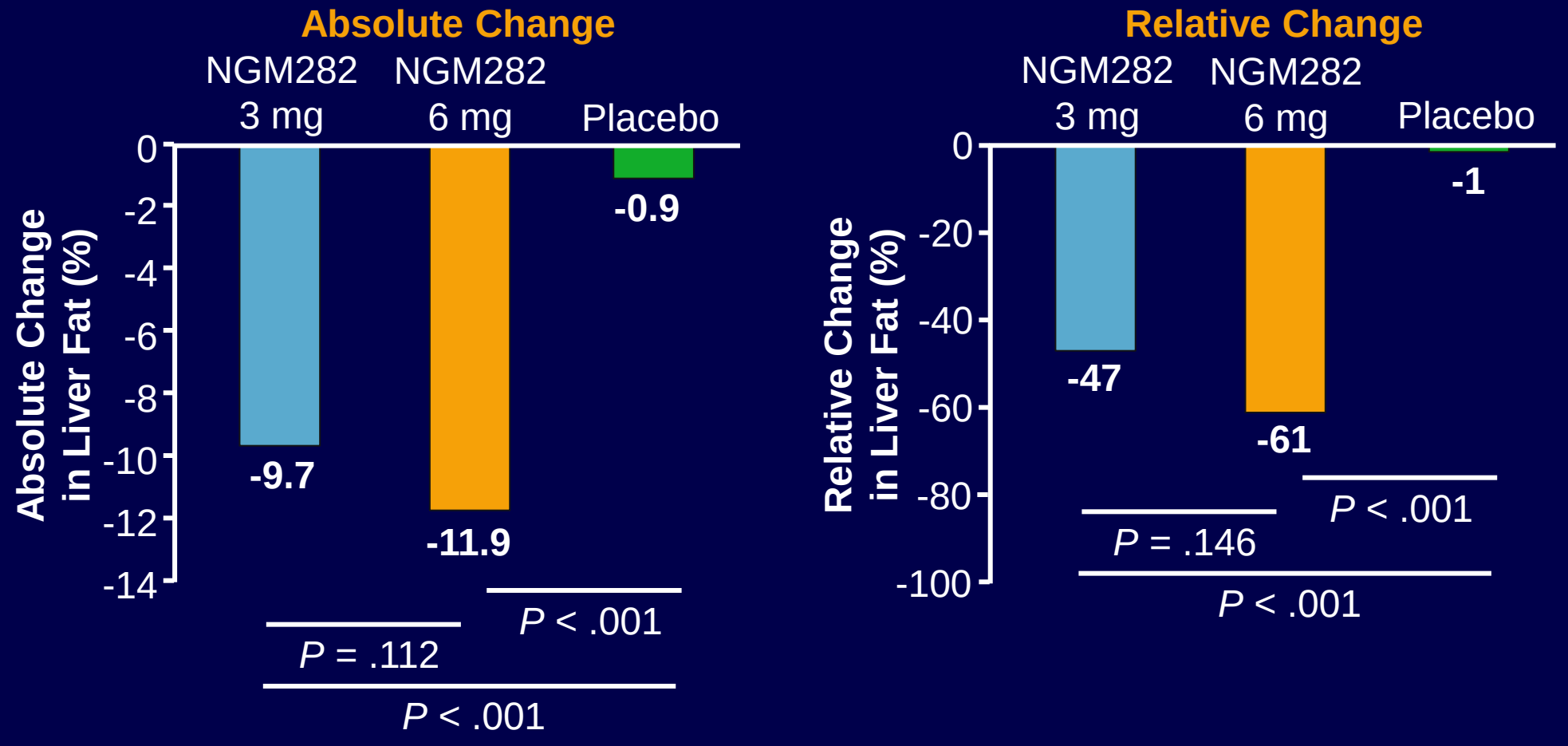
NGM282 Primary Endpoint: Absolute and Relative Change in Liver Fat Content at Wk 12

- Significant reduction in liver fat content vs placebo by MRI-PDFF



Harrison SA, et al. EASL 2017. Abstract LBO-07.

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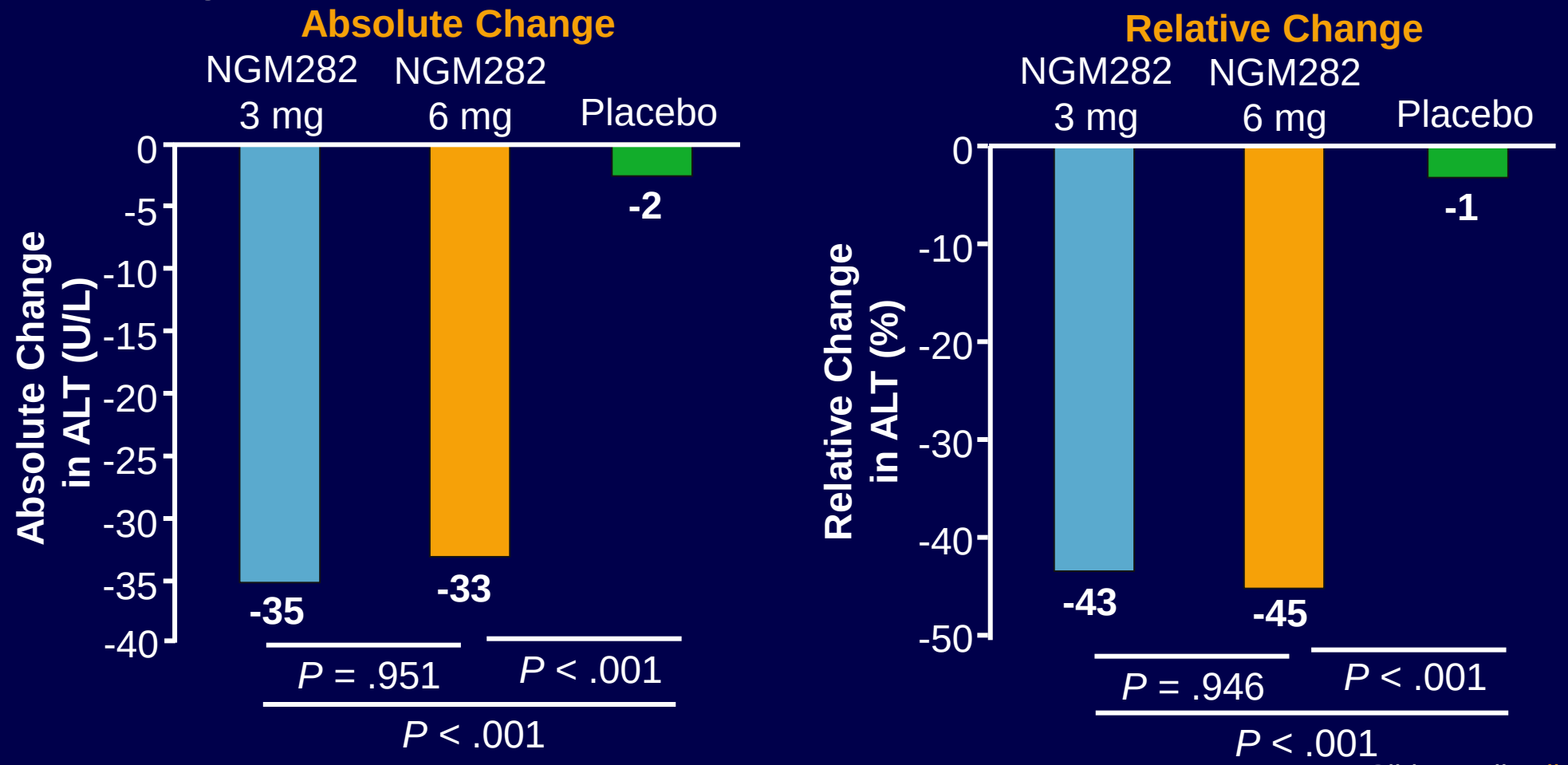
NGM282: Absolute and Relative Change in ALT at Wk 12

- Similar significant decreases observed with AST



Harrison SA, et al. EASL 2017. Abstract LBO-07.

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NGM282: Safety

- Most TEAEs grade 1[1]
- Serious AEs, n = 1[1]
  - Acute pancreatitis, possibly related to treatment
- Significant LDL increase at Wk 12 with 3 mg or 6 mg but not placebo ($P < .001$)[1]
  - Rapidly mitigated by statins in preclinical study[2]

TEAEs Occurring in > 10% of Pts, n (%)[1]	NGM282 3 mg (n = 27)	NGM282 6 mg (n = 28)	Placebo (n = 27)
ISRs	11 (40.7)	15 (53.6)	2 (7.4)
Diarrhea/loose stools	11 (40.7)	10 (35.7)	6 (22.2)
Abdominal pain	8 (29.6)	5 (17.9)	2 (7.4)
Nausea	9 (33.3)	4 (14.3)	1 (3.7)
Headache	3 (11.1)	5 (17.9)	5 (18.5)
Abdominal distension	3 (11.1)	4 (14.3)	1 (3.7)
Vomiting	2 (7.4)	5 (17.9)	0
Frequent bowel movements	3 (11.1)	1 (3.6)	2 (7.4)
Increased appetite	2 (7.4)	4 (14.3)	0
Constipation	3 (11.1)	1 (3.6)	1 (3.7)
Injection site bruising	2 (7.4)	0	3 (11.1)
Weight decrease	0	3 (10.7)	0

1. Harrison SA, et al. EASL 2017. Abstract LBO-07. 2. Luo J, et al. EASL 2017. Abstract FRI-353.

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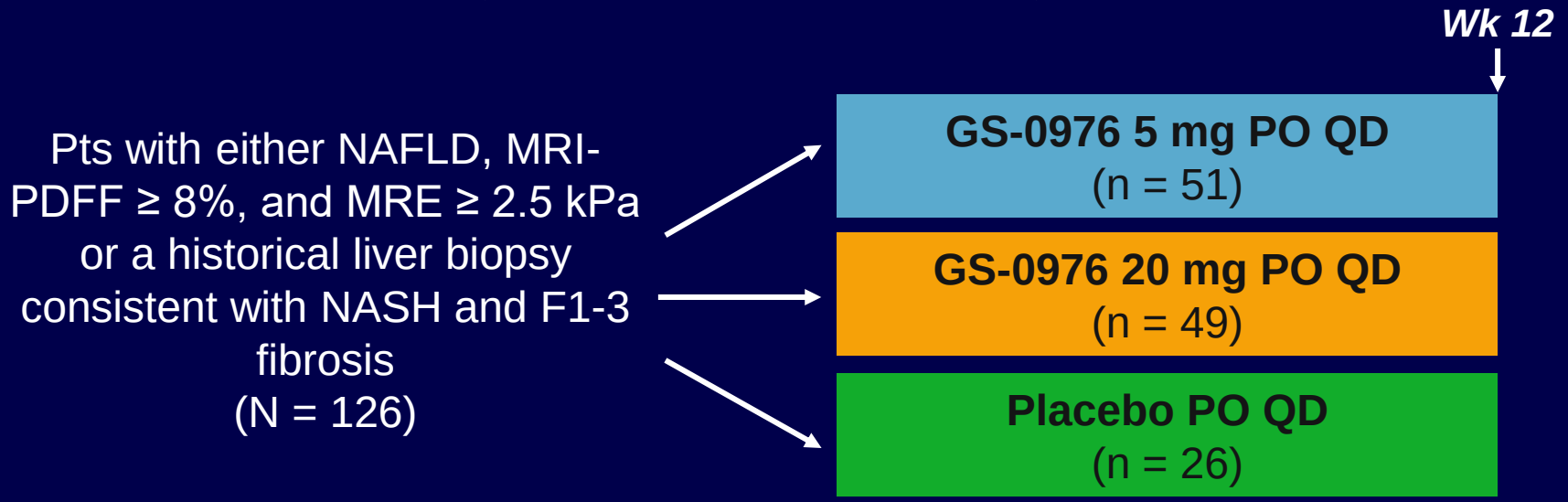
GS-0976:
ACC Inhibitor

GS-0976 in Pts With NASH

- Randomized, double-blind, placebo-controlled phase II study
  - 65% female, 60% with diabetes, 40% with advanced fibrosis (≥ F3)



- Endpoints: MRI-PDFF, MRE, *FibroScan*, and serum fibrosis markers

Loomba R, et al. AASLD 2017. Abstract LB-9. ClinicalTrials.gov. NCT02856555.

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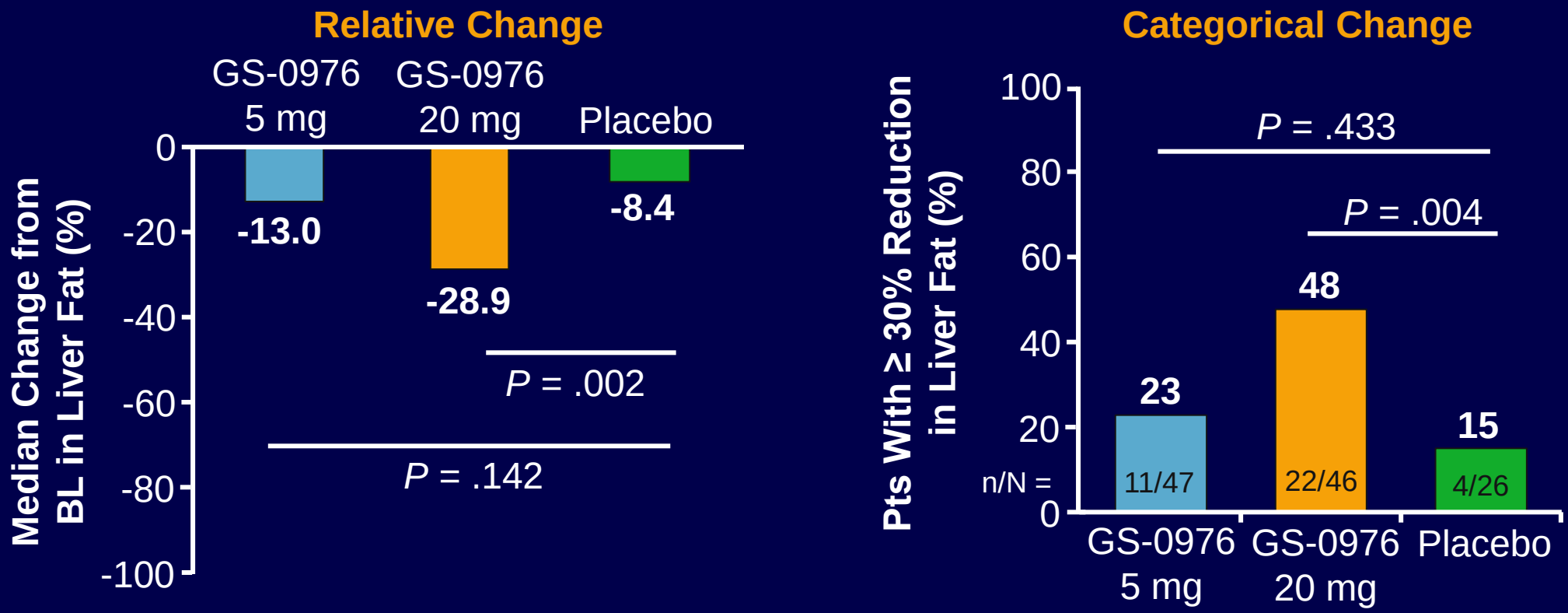
GS-0976: Relative and Categorical Change in Liver Fat Content at Wk 12

- Statistically significant decrease in liver fat content with 20 mg, but not 5 mg, vs placebo by MRI-PDFF



Loomba R, et al. AASLD 2017. Abstract LB-9. These data are available in unpresented abstract format only and will be presented in full during the AASLD meeting. We encourage you to review the presented data before making any conclusions.

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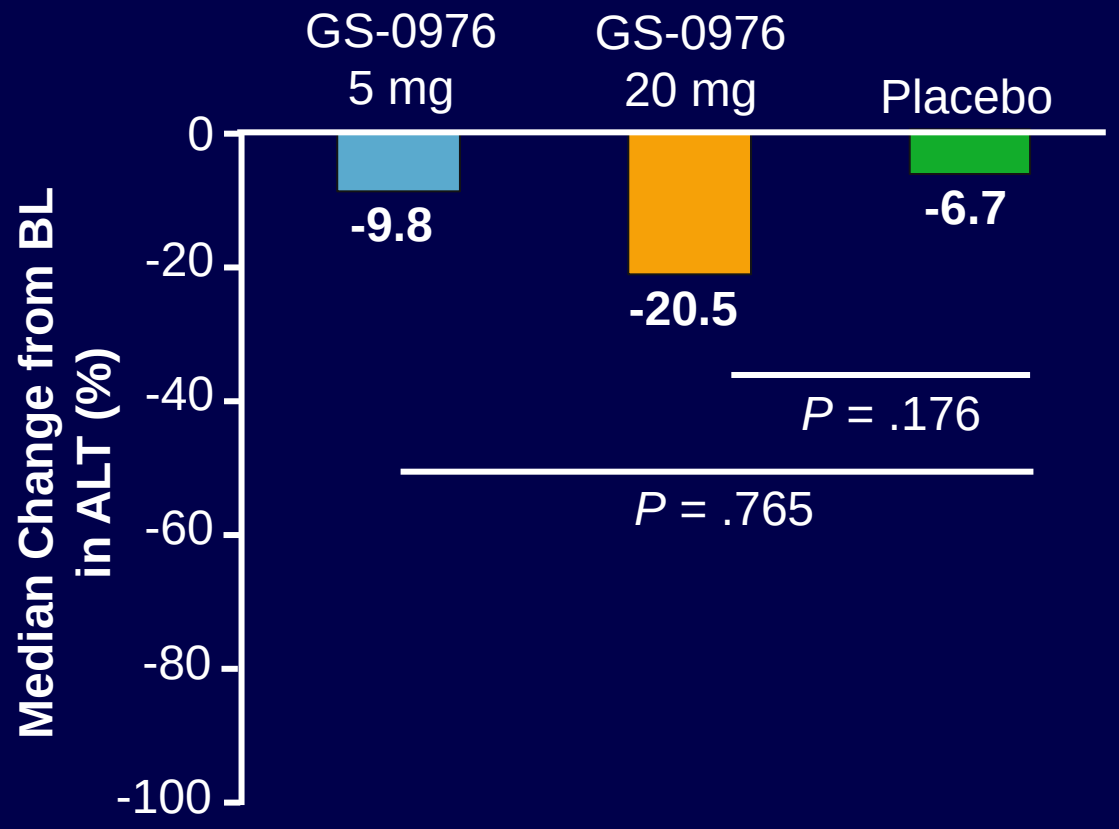
GS-0976: Relative Change in ALT at Wk 12

- No statistically significant decrease in ALT vs placebo



Loomba R, et al. AASLD 2017. Abstract LB-9. These data are available in unpresented abstract format only and will be presented in full during the AASLD meeting. We encourage you to review the presented data before making any conclusions.

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GS-0976: Safety

Safety Event	GS-0976 5 mg (n = 51)	GS-0976 20 mg (n = 49)	Placebo (n = 26)
Median relative change in TG, %	13	11	-4
Asymptomatic grade 3/4 TG elevation, n	9	7	NR

- Grade 3/4 TG elevation predicted by BL TG > 250 mg/dL ($P < .001$)
  - Response to fibrate or fish oil, n = 4
  - Resolution without treatment or study drug cessation, n = 7

Loomba R, et al. AASLD 2017. Abstract LB-9. These data are available in unpresented abstract format only and will be presented in full during the AASLD meeting. We encourage you to review the presented data before making any conclusions.

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