

# **Hepatic Proton Density Fat Fraction Correlates With Histologic Measures of Steatosis and Is Responsive to Changes in Those Measures in a Multi-center Nonalcoholic Steatohepatitis Clinical Trial**

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# Disclosures (Dr. M. Middleton)

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- ◆ Consultation or contracted laboratory services through UCSD: Alexion, AstraZeneca, Biomedical Systems, Bristol-Myers Squibb, Celgene, Galmed, Genentech, General Electric, Genzyme, Gilead, Guerbet, Icon, Intercept, Janssen, Keosys, NuSirt, Perspectum, Pfizer, Profil, Sanofi, Shire, Siemens, Synageva, Takeda, VirtualScopics

# Introduction

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- ◆ Proton density fat fraction (PDFF) estimated by MRI is a noninvasive biomarker of hepatic steatosis<sup>1</sup>
- ◆ MRI-PDFF correlates with histologic grade of hepatic steatosis<sup>2</sup>
  - $\geq 30\%$  relative decrease in PDFF has been associated with a histologic response in NASH<sup>2,3</sup>
- ◆ Selonsertib (SEL; formerly GS-4997) is a selective inhibitor of apoptosis signal-regulating kinase 1 (ASK1) being studied for the treatment of NASH (NCT02466516)

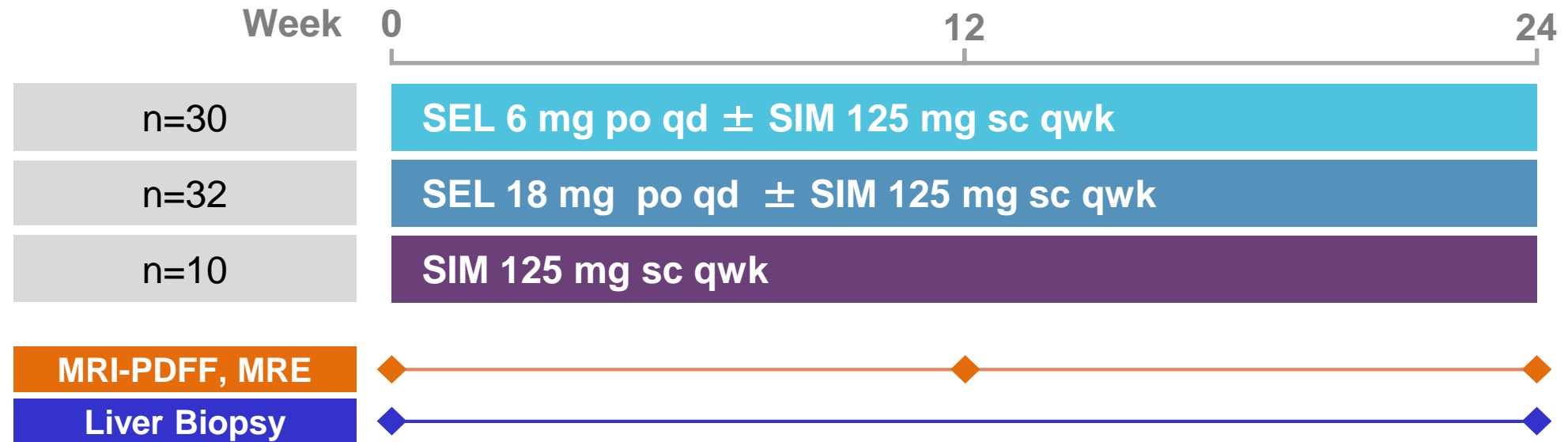
1. Dulai PS, et al. *J Hepatol* **2016**; 65:1006-1016  
2. Patel J, et al. *Ther Adv Gastroenterol* **2016**; 9:692-701  
3. Lawitz, E, et al. *EASL* **2017**; GS-009.

# Objectives

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- ◆ To examine correlations between hepatic MRI-PDFF and histologic measures of steatosis
- ◆ To assess associations between changes in hepatic MRI-PDFF, liver histology, and biochemical measures

# Study Design<sup>1</sup>



- ◆ Key inclusion criteria<sup>1</sup>
  - Biopsy-proven NASH with NAS  $\geq 5$   
( $\geq 1$  point for steatosis, lobular inflammation, hepatocellular ballooning)
  - F2-F3 fibrosis
- ◆ Treatment groups combined for this analysis<sup>2</sup>

NAS - NAFLD Activity Score; PDFF - proton density fat fraction; MRE - magnetic resonance elastography; SEL - Selonsertib; SIM - Simtuzumab

1. Loomba R, et al. AASLD 2016; LB-03. 2. Harrison S, et al. EASL 2017; PS-094

# Assessment Methods

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## Imaging

- MRI-PDFF
  - Hepatic steatosis
  - Colocalized regions of interest (9 Couinaud segments)
- MRE
  - Liver stiffness
  - 2D, 60 Hz

- ◆ Standardized and centrally read (UC San Diego)

## Histology

- NAS
- Fibrosis according to NASH CRN system
- Morphometry for hepatic fat and collagen

- ◆ Centrally read (Dr Z. Goodman)

# Study Endpoints

Imaging Responses	MRI-PDFF	≥ 30% reduction in MRI-estimated PDFF <sup>1,2</sup>
	MRE	≥ 15% reduction in MRE-estimated liver-stiffness <sup>3</sup>
Histologic Responses	NAS	≥ 2-point reduction
	Steatosis Lobular inflammation Hepatocellular ballooning	≥ 1-grade reduction
	Fibrosis	≥ 1-stage reduction
Serum Markers	Cell death	CK18 (M30 and M65)
	Metabolic	Glucose, HbA1c, cholesterol

PDFF - proton density fat fraction; MRE - magnetic resonance elastography; NAS - NAFLD Activity Score; CK - cytokeratin

1. Lawitz E, et al. EASL 2017; GS-009; 2. Patel J, et al. *Ther Adv Gastroenterol* 2016; 9:692-701; 3. Loomba R, et al. EASL 2017; SAT-489.

# Statistical Analyses

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- ◆ Correlations between MRI-PDFF and other variables assessed using Spearman correlation coefficients ( $r_s$ )
- ◆ Relative reductions from baseline in MRI-PDFF with histologic variables of steatosis, lobular inflammation, ballooning, and NAS using Kruskal-Wallis tests
- ◆ Changes in morphometric fat and serum markers compared between MRI-PDFF responders and nonresponders using Kruskal-Wallis tests



# Results

## Demographics and Baseline Characteristics by MRI-PDFF Response

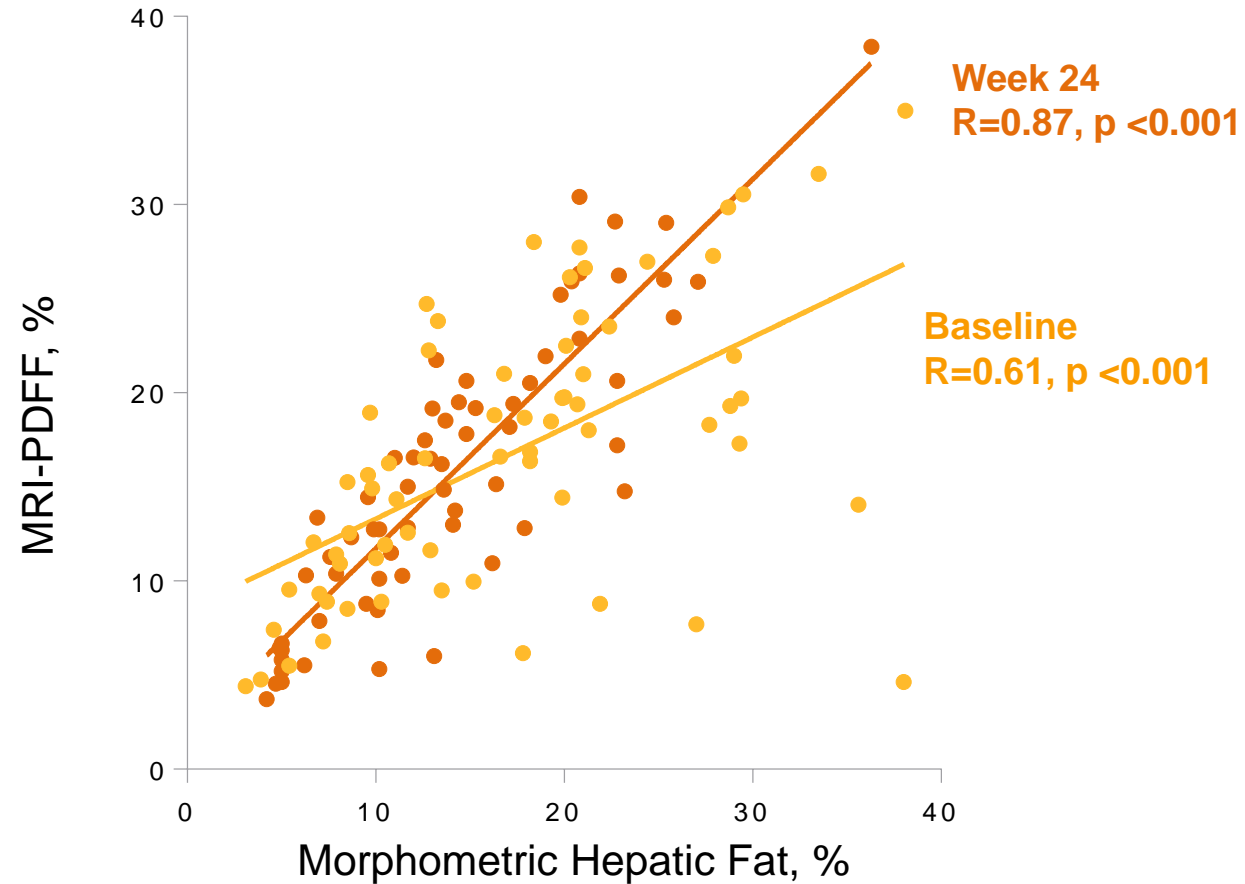
		<30% Reduction in PDFF n=53	≥30% Reduction in PDFF n=12	Total n=65
<b>Demographics</b>	Age, y	55 (47, 61)	59 (48, 63)	56 (47, 62)
	Female, n (%)	37 (70)	9 (75)	46 (71)
	White, n (%)	47 (89)	12 (100)	59 (91)
	BMI, kg/m <sup>2</sup>	33.4 (29.5, 37.3)	31.6 (27.0, 35.9)	32.9 (29.4, 37.3)
<b>Metabolic</b>	Diabetes, n (%)	38 (72)	7 (58)	45 (69)
	Glucose, mg/dL	115 (97, 149)	112 (99, 154)	115 (97, 149)
	Cholesterol, mg/dL	188 (166, 210)	191 (168, 210)	188 (166, 210)
	HbA1c, %	6.6 (5.8, 7.9)	6.0 (5.6, 7.7)	6.4 (5.8, 7.9)
<b>Liver Biochemistry</b>	ALT, U/L	58 (47, 88)	54 (34, 89)	58 (47, 88)
	GGT, U/L	57 (35, 85)	46 (39, 59)	54 (37, 80)
<b>Cell Death Markers</b>	CK18 (M30), U/L	547 (311, 850)	428 (230, 897)	511 (267, 863)
	CK18 (M65), U/L	808 (447, 1465)	618 (222, 1319)	738 (370, 1379)

BMI - body mass index; ALT - alanine aminotransferase; GGT - gamma-glutamyltransferase; CK - cytokeratin

# Baseline Histology and Imaging by MRI-PDFF Response

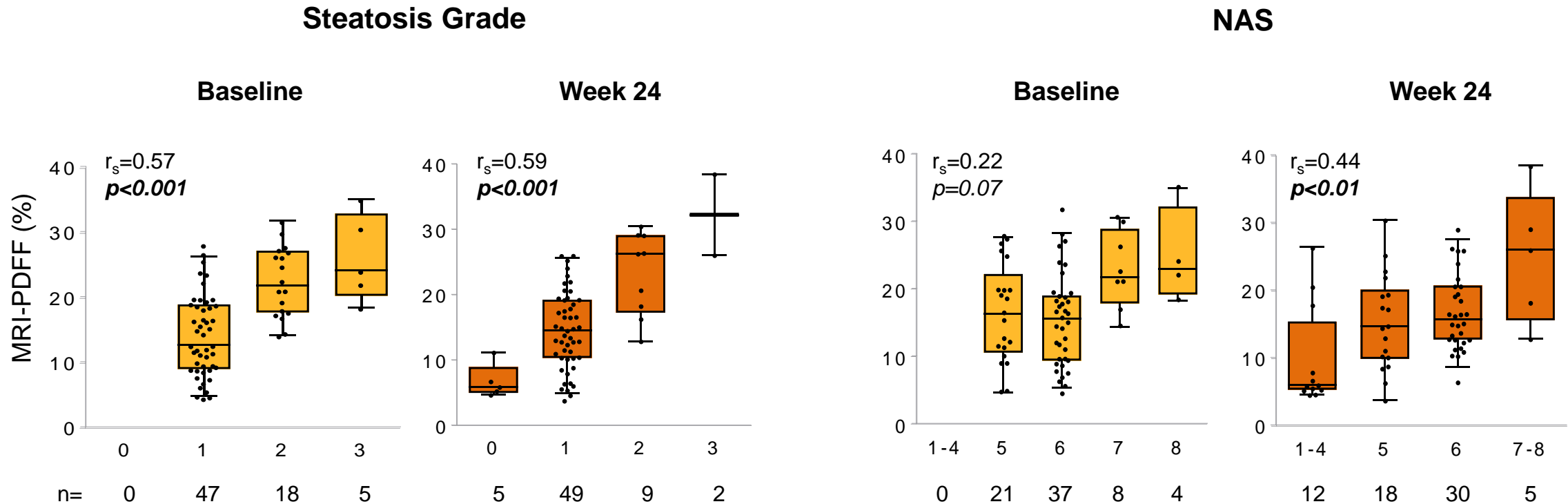
		<30% Reduction in PDFF n=53	≥30% Reduction in PDFF n=12	Total n=65
<b>Histology</b>	F3 (vs F2) fibrosis, n (%)	35 (66)	9 (75)	44 (68)
	NAS 7–8, n (%)	9 (17)	3 (25)	12 (19)
	Steatosis (Grades 2–3), n (%)	17 (32)	4 (33)	21 (32)
	Lobular inflammation (Grade 3), n (%)	37 (70)	7 (58)	44 (68)
	Hepatocellular ballooning (Grade 2), n (%)	46 (87)	10 (83)	56 (86)
	Morphometric hepatic fat, %	17.8 (9.8, 21.3)	18.4 (11.8, 21.4)	17.8 (10.0, 21.3)
<b>Imaging</b>	MRI-PDFF, %	16.5 (10.9, 22.0)	19.2 (11.0, 22.4)	16.6 (10.9, 22.0)
	MRE, kPa	3.7 (3.1, 4.6)	4.1 (3.0, 4.7)	3.7 (3.1, 4.6)

# Association Between MRI-PDFF and Percent Morphometric Hepatic Fat



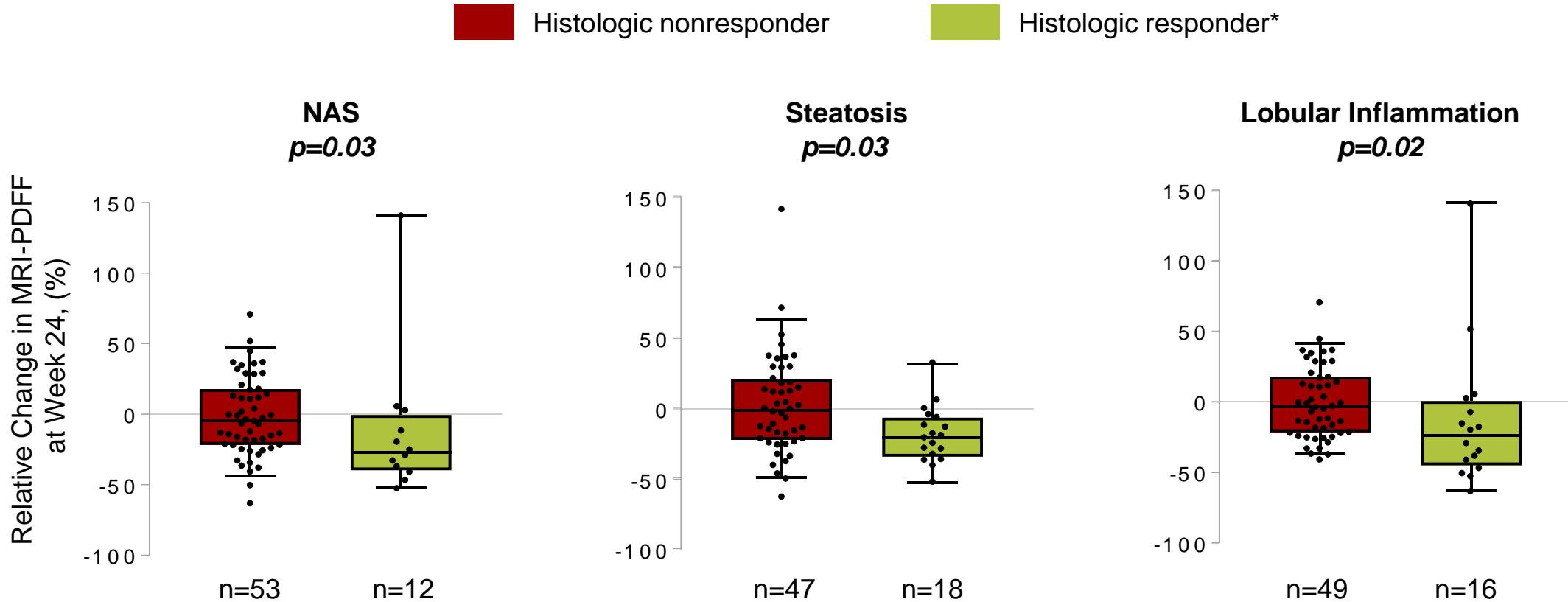
- ◆ MRI-PDFF was significantly correlated with percent morphometric hepatic fat at Baseline and Week 24

# Association Between MRI-PDFF, and Steatosis and NAS



- ◆ MRI-PDFF associated with histologic grade of steatosis and NAS at Baseline and at Week 24
  - No associations were observed with lobular inflammation or ballooning

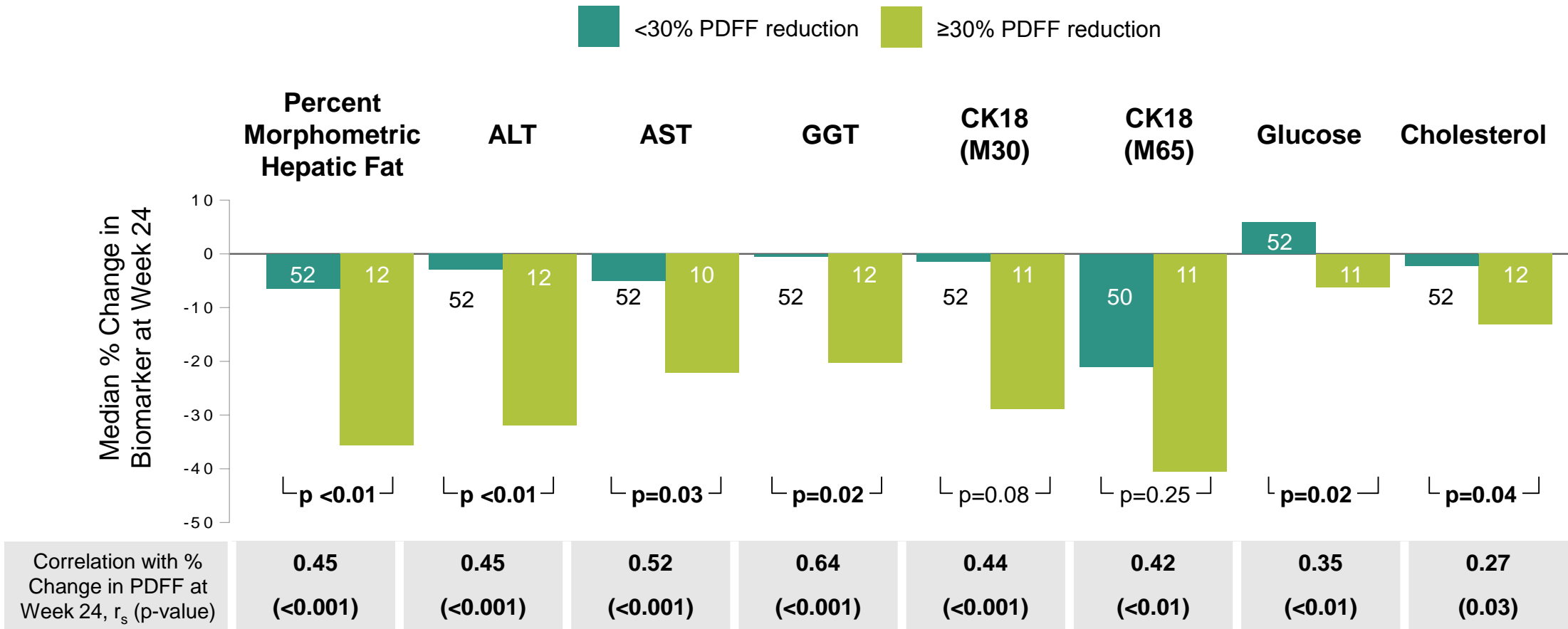
# Changes in MRI-PDFF in Histologic Nonresponders vs. Responders



- ◆ Patients with improvements in NAS, steatosis, and lobular inflammation had greater reductions in MRI-PDFF

\*NAS response defined as  $\geq 2$ -point reduction; steatosis and lobular inflammation responses defined as  $\geq 1$ -grade reduction.

# Associations Between Changes in Biomarkers and MRI-PDFF Response



- ◆ PDFF response at Week 24 was associated with reductions in hepatic fat content, liver biochemistry, CK18, glucose, and cholesterol

# Conclusions

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- ◆ Hepatic steatosis estimated by MRI-PDFF was correlated with histologic measures of steatosis, including steatosis grade, NAS, and morphometric fat content
- ◆ Relative reductions in MRI-PDFF were associated with improvements in steatosis, NAS, lobular inflammation, and relevant serum markers
- ◆ These data help further confirm and validate MRI-PDFF as a biomarker of hepatic steatosis and support its utility as a noninvasive endpoint for evaluation of NASH treatment

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