

# The role of reduction in liver fat content (MRI-PDFF) and ALT in predicting treatment response in NASH: A secondary analysis of the randomized, controlled BALANCED trial

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## INTRODUCTION

Efruxifermin (EFX) is a long-acting Fc-FGF21 analogue being developed as a potential therapy for patients with non-alcoholic steatohepatitis (NASH) and fibrosis. In the phase 2a BALANCED study (ClinicalTrials.gov NCT03976401) in patients with biopsy-confirmed NASH (F1-3), EFX treatment resulted in significantly greater reduction in liver fat content (LFC) compared to placebo as assessed by MRI-PDFF at 12 weeks, and was associated with NASH resolution and fibrosis improvement on histology following 16 weeks of treatment (liver biopsies assessed between Week 16 and Week 22)<sup>1</sup>. This analysis is performed in a subset of patients who had both MRI-PDFF at baseline and week 12, and baseline and end-of-treatment liver biopsies (n=42; n=40 on EFX and n=2 placebo). All 42 patients achieved a ≥30% relative reduction in LFC at week 12, and response to histologic endpoints was compared for ALT responders (ALT decline ≥ 17U/L) and ALT non-responders (ALT decline < 17U/L), as well as ALT responders who achieved normalization of liver fat (LFC ≤5% by MRI-PDFF).

## AIMS

The aim of this analysis was to examine the utility of a threshold response for ALT (ALT decline ≥ 17U/L) with or without normalization of LFC in predicting histologic improvements among a treated population who achieved a ≥30% relative reduction of liver fat.

## METHODS

Figure 1. Study Design

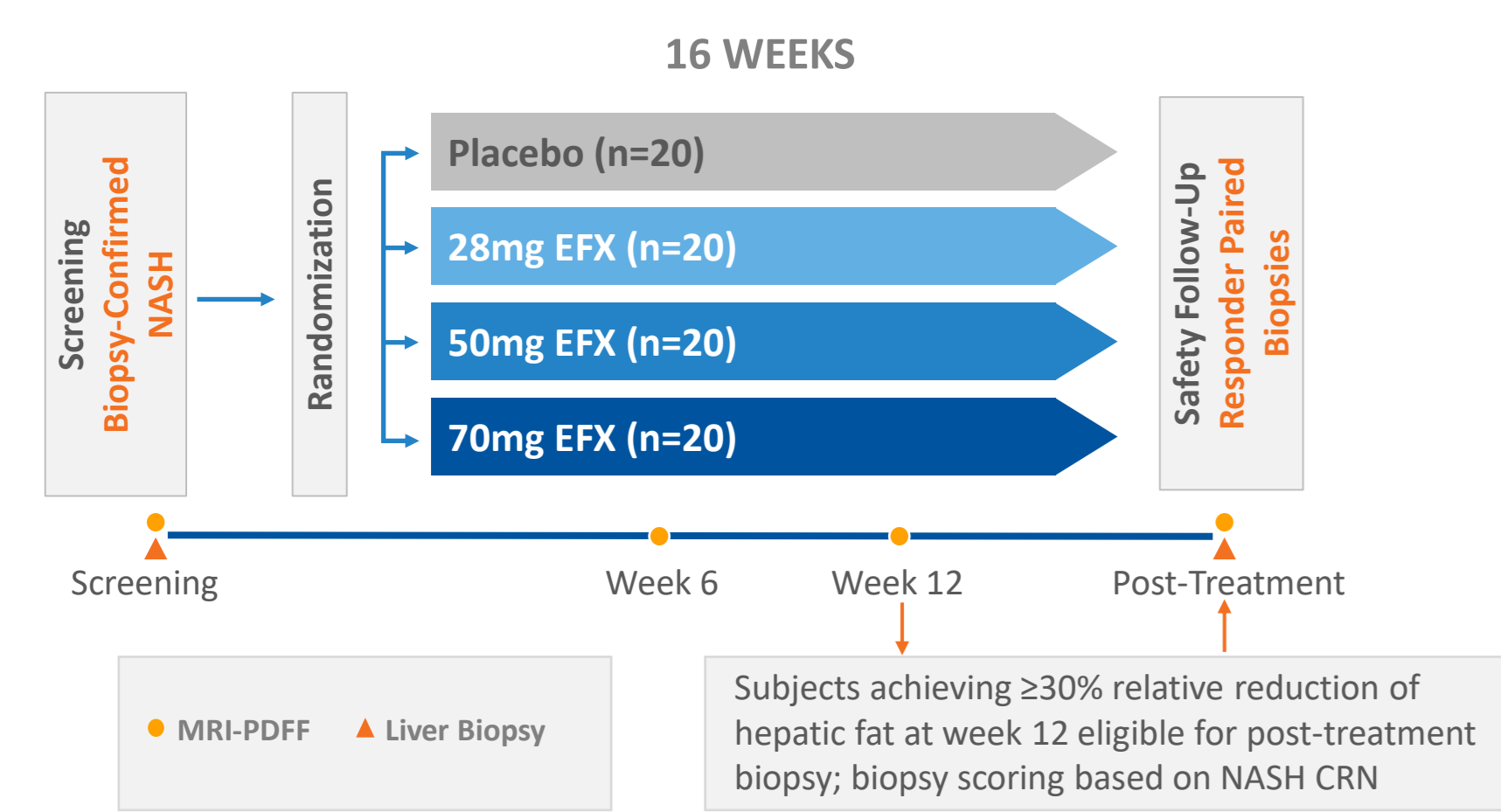
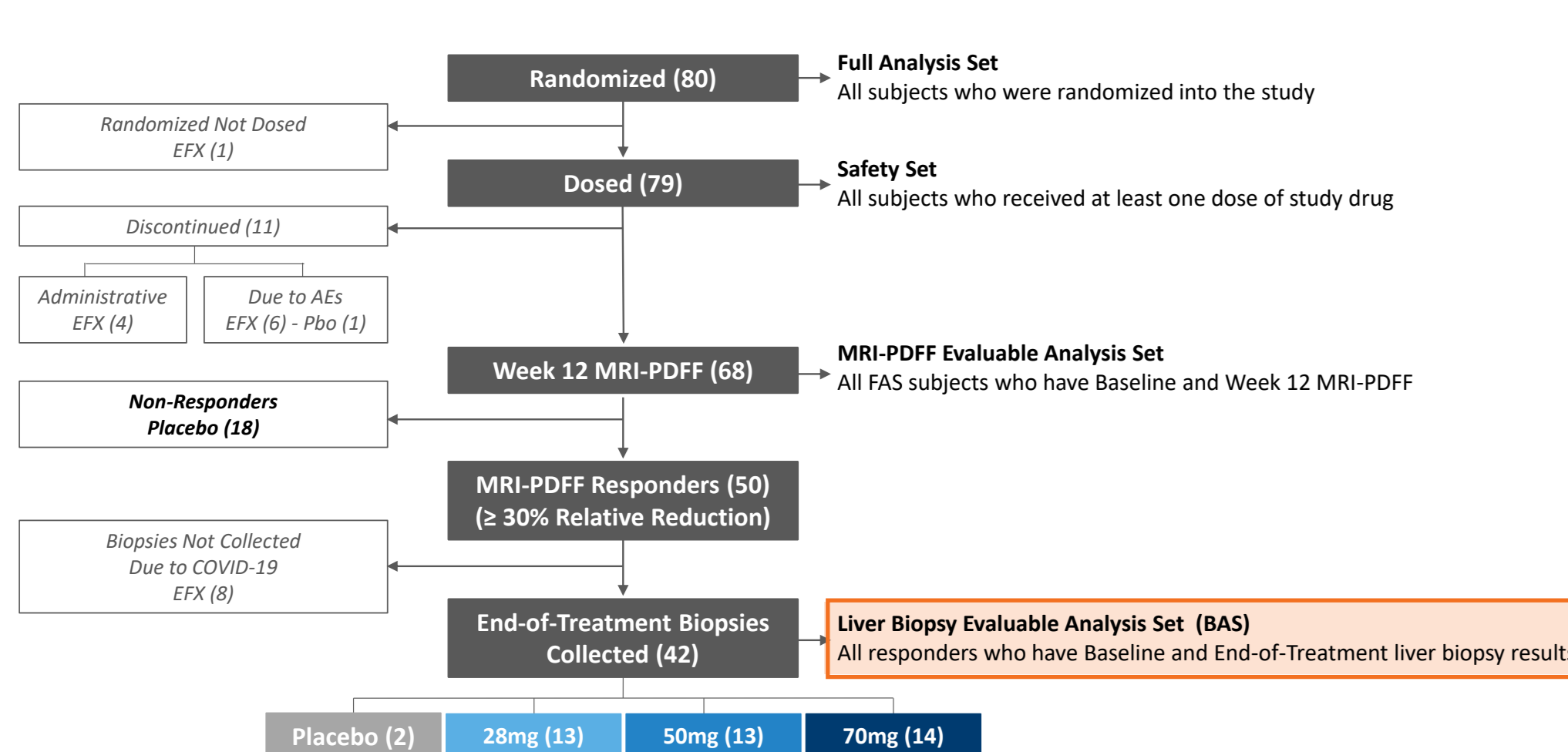


Figure 2. Patient Disposition



## RESULTS

Table 1. Change in Liver Fat Content and ALT

Liver Fat Content (LFC) <sup>1,2</sup>		
	Placebo	All EFX
Absolute change from baseline at Week 12, mean <sup>a</sup>	-0.18	-14.08
Relative (%) change from baseline at Week 12, mean <sup>a</sup>	0.14	-70.557
MRI-PDFF Responders (≥ 30% reduction in LFC) at Week 12 <sup>b</sup>	2 (10%)	48 (100%)
Proportion of patients with normalization of LFC (≤ 5%), n (%) <sup>b</sup>	1 (5%)	23 (48%)
Patients with LFC normalization in BAS <sup>c</sup> , n	1	15

ALT <sup>1</sup>		
	Placebo	All EFX
Absolute change from baseline at Week 12	-1.08	-28.33
Relative (%) change from baseline at Week 12	-1.88	-42.34
Proportion of ALT Responders (≥ 17 U/L reduction in ALT), n (%)	1 (5%)	30 (51%)
ALT Responders in BAS, n	1	27

<sup>a</sup>Full Analysis Set (N=80; N=21 Placebo; N=59 EFX); <sup>b</sup>MRI-PDFF Evaluable Analysis set (N=68; N=20 placebo; N=48 EFX); <sup>c</sup>Biopsy Analysis Set (N=42; N=2 Placebo and N=40 EFX)

Table 2. Demographics and Baseline Characteristics by ALT Response

Parameter	ALT Responders (N=28)	ALT Non-responders (N=14)
Age (Years)	52	54
Sex (% Female)	43	64
Ethnicity (% Hispanic)	57	64
BMI (kg/m <sup>2</sup> )	36.9	35.5
Body weight (kg)	106	94
Type 2 Diabetes, n (%)	14 (50)	6 (43)
Liver Fat Content (% by MRI-PDFF)	18.9	19.6
NAFLD Activity Score (NAS)	5.5	5.4
Alanine Aminotransferase (ALT) (U/L)	65.93	36.64
Aspartate Aminotransferase (AST) (U/L)	47.05	26.11
Fibrosis Stage F2/F3, n (%)	15 (53.6)	9 (64.3)
Pro-C3 (µg/mL)	17.95	13.99
ELF Score	9.72	9.36

Table 3. ALT Response is Associated with Greater Probability of Substantial Reduction of Liver Fat

Parameter	Proportion of Patients Achieving Fat Reduction Thresholds at Week 12 <sup>d</sup>		
	≥50% Reduction, n(%)	≥70% Reduction, n (%)	Normalization of LFC (≤5%)
ALT Responders (N=34)	30 (94)	22 (69)	17 (53)
ALT Non-responders (N=32)	12 (35)	8 (24)	7 (21)
Odds Ratio Responders Vs Non-responders (95% CI)	27.5 (5.581, 135.507)	7.150 (2.406, 21.252)	4.371 (1.480, 12.913)
P Value	<0.0001	0.0004	0.0099

<sup>d</sup>Patients with available MRI-PDFF and ALT change at Week 12 (N=66)

## CONCLUSIONS

- EFX treatment for 12 weeks elicited unprecedented reduction in liver fat content of F1-F3 NASH patients.
- Achieving a threshold for reduction of ALT of ≥17U/L was associated with
  - greater probability of substantially decreasing or normalizing liver fat content
  - a greater proportion of patients, with or without LFC normalization, achieving resolution of NASH
- The accuracy of predicting resolution of NASH was reasonable (AUROC ≥0.74) using a threshold of ≥17U/L, and enhanced by combining with LFC normalization
- Reducing ALT did not appear to predict regression of fibrosis. This may be a consequence of:
  - the short treatment period in the context of turnover of fibrotic structures
  - and/or inhibition of fibrosis by EFX independent of improvements in hepatocyte health

Figure 3. More ALT responders with or without normalization of LFC improved histologically compared to ALT non-responders, with the exception of fibrosis

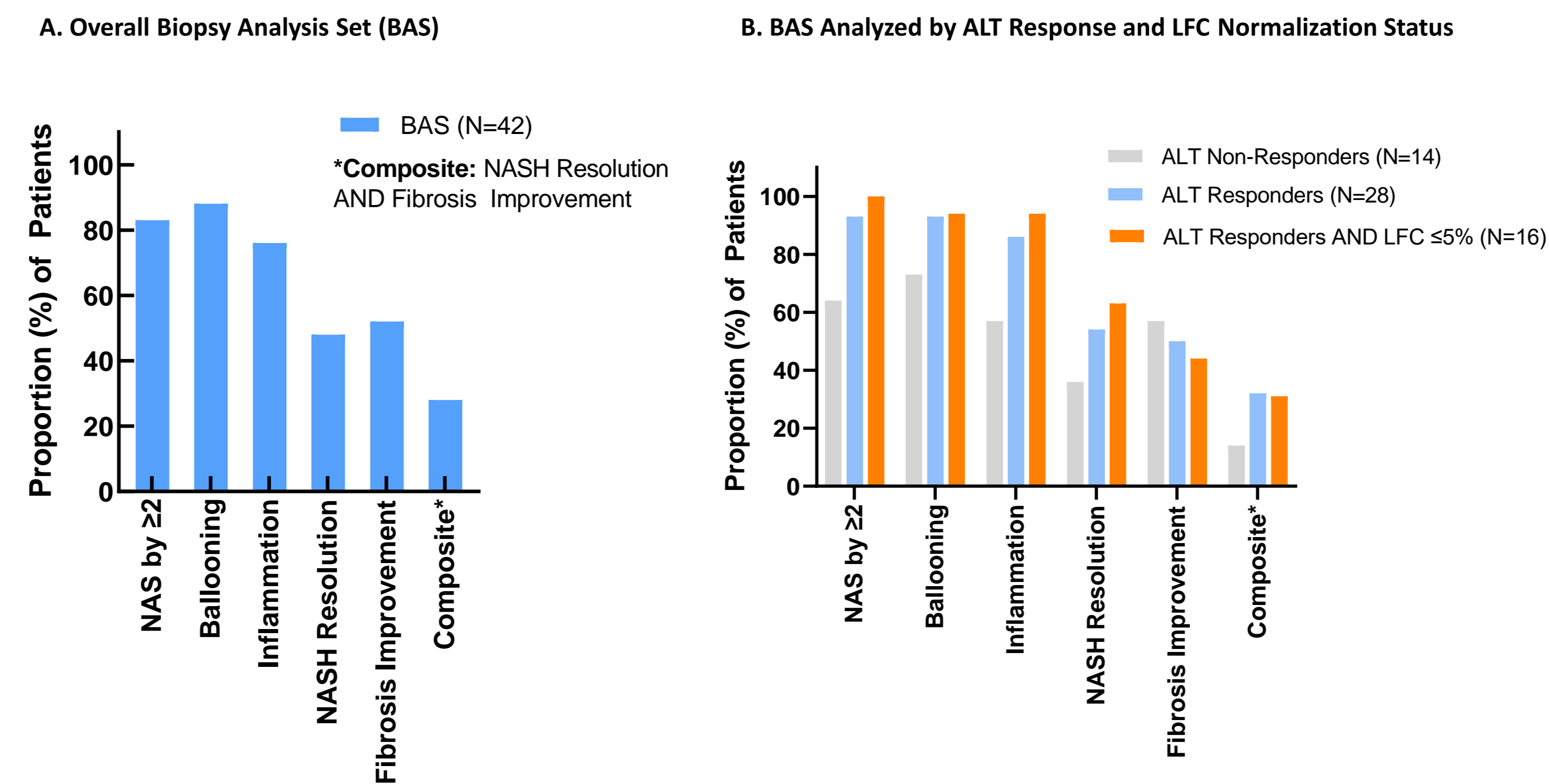


Table 4. AUROC for Predicting Histologic Response Among MRI-PDFF Responders With Available Histology

Histologic Response	ALT Responders (N=28)		ALT Responders With LFC ≤5% (N=16)	
	AUROC	95% CI	AUROC	95% CI
Improvement in NAS by ≥2 <sup>a</sup>	0.8654	0.5876, 1.0000	NE	NE
Improvement in Ballooning by ≥1	0.8558	0.6802, 1.0000	0.9333	0.8027, 1.0000
Improvement in Inflammation by ≥1	0.4323	0.2231, 0.6415	0.4667	0.2503, 0.7280
NASH Resolution	0.741	0.5561, 0.9260	0.825	0.6070, 1.0000
Improvement in Fibrosis by ≥1	0.6046	0.3829, 0.8263	0.7063	0.4246, 0.9881
NASH Resolution and Improvement in Fibrosis by ≥1	0.6228	0.3904, 0.8552	0.7941	0.898, 0.217

<sup>a</sup>At least 1 point improvement in ballooning or inflammation; LFC: liver fat content; NE: Not Evaluable

Figure 4. Likelihood of Achieving Histologic Response by ALT Response Status (Among MRI-PDFF Responders)

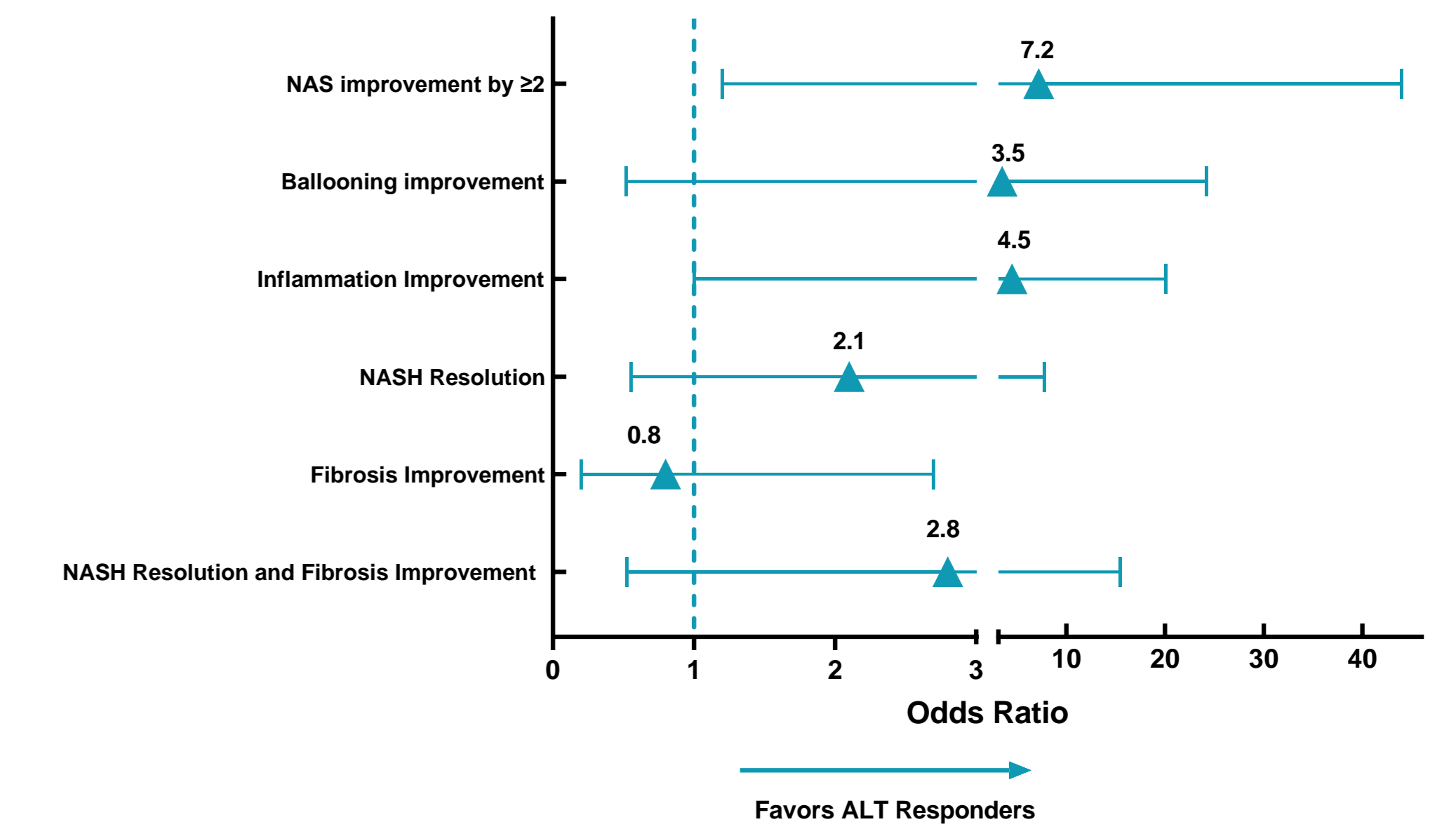
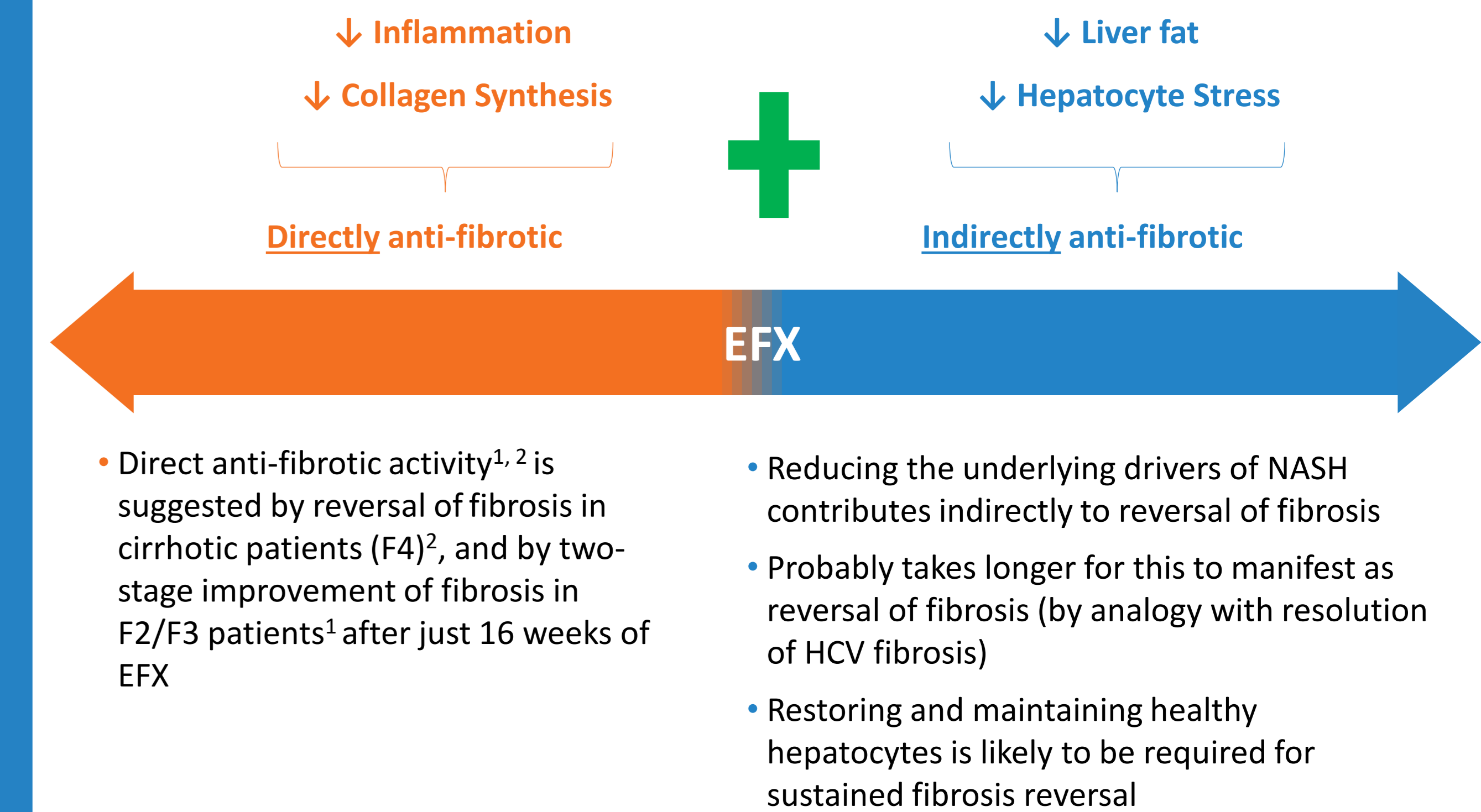


Figure 5. Why reduction in ALT does not correlate with fibrosis improvement

- Following 16 weeks of EFX treatment<sup>1</sup>: 22(55%) of 40 patients achieved ≥1 stage, and 11 (50%) of 22 F2/F3 patients achieved ≥ 2 stage improvement<sup>1</sup>.



- Direct anti-fibrotic activity<sup>1,2</sup> is suggested by reversal of fibrosis in cirrhotic patients (F4)<sup>2</sup>, and by two-stage improvement of fibrosis in F2/F3 patients<sup>1</sup> after just 16 weeks of EFX
- Reducing the underlying drivers of NASH contributes indirectly to reversal of fibrosis
- Probably takes longer for this to manifest as reversal of fibrosis (by analogy with resolution of HCV fibrosis)
- Restoring and maintaining healthy hepatocytes is likely to be required for sustained fibrosis reversal

## ACKNOWLEDGMENTS

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## REFERENCES

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