Paris NASH Meeting

International Think Tank

September 7 & 8, 2023, Institut Pasteur

SCIENTIFIC PROGRAMME

International Think Tank

UNIVERSITÄTSmedizin. MAINZ
Schwerpunkt Metabolische Lebererkrankungen

Markers of Treatment Response

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LITMUS LIVERSCREEN imi innovative medicines initiative

Rhein-Main Universitäten
Eine strategische Allianz

Disclosure

Advisor to Astra Zeneca, Apollo Endosurgery, Bayer, Boehringer Ingelheim, Gilead Sciences, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Siemens Healthineers.

Grant & research support from Gilead, Boehringer Ingelheim, Siemens Healthcare GmbH

Sp*eaker honorarium* from Boehringer Ingelheim, Echosens, Novo Nordisk, Madrigal Pharmaceuticals, Histoindex, MedPublico GmbH

Reaching Goals in MASLD treatment

Where do we want to be?

PARIS NASH 2023

HOW TO ASSESS DRUG RESPONSE?

Revisiting Biomarker

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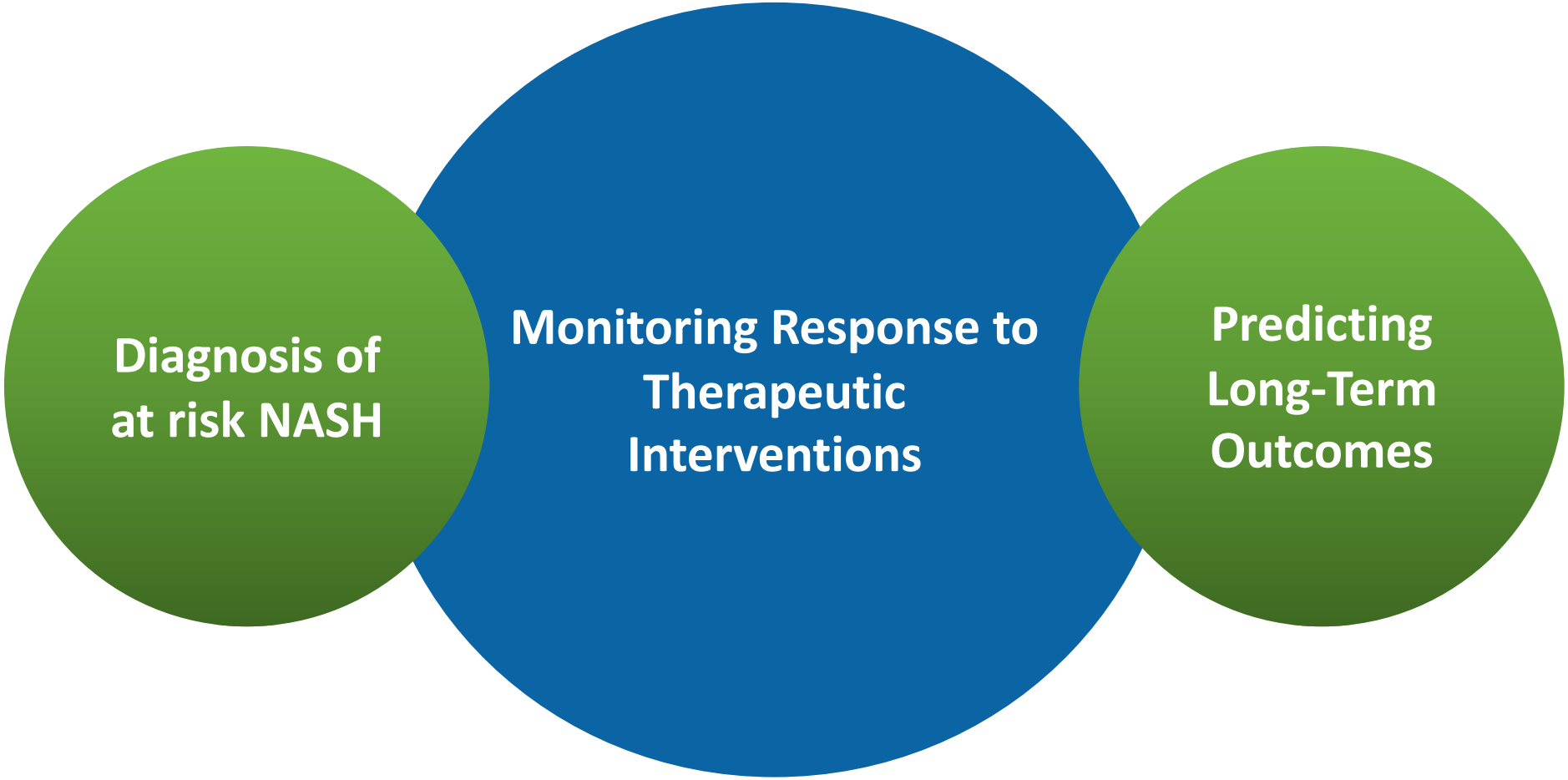

LESSONS LEARNED FROM FAILURES

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We can utilize the data of responder vs non-responder!

Table 1. Drugs that have been (temporarily) withdrawn from seeking marketing authorization for NASH.

Company	Drug	Drug class	Phase	Reason	Date of announcement of discontinuation
Gilead	Selonsertib	ASK1 inhibitor	3	Lack of efficacy	2/11/2016
Gilead	Simtuzumab	LOXL2 neutralizing antibody	2	Lack of efficacy	2/11/2016
Cempra	Solithromycin	CCL24 neutralizing antibody	1	Hepatotoxicity	28/2/2017
Astra Zeneca	AZD4076 (RG-125)	Anti micro RNA-103/107	1/2a	Unclear	12/6/2017
Gilead	Firsocostat (monotherapy)	Acetyl-CoA carboxylase (ACC1/ACC2) inhibitor	3	Efficacy	16/12/2019*
Gilead	Cilofexor (monotherapy)	Farnesoid X receptor agonist	3	Efficacy	16/12/2019*
Boehringer Ingelheim	BI 1467335	Amine oxidase copper-containing 3 (AOC3) inhibitor	2	Drug-drug interactions	18/12/2019
Conatus	Emricasan	Pan-caspase inhibitor	2b	Efficacy	24/6/2019
Genfit	Elafibranor	PPAR-α/δ agonist	3	Efficacy	23/7/2020
TaiwanJ Pharmaceuticals	JKB-121	Toll-like receptor 4 antagonist	2	Efficacy	19/4/2018
Temporary halt					

* A future phase 3 clinical trial with combination of these two compounds – without selonsertib is in current development.

Joost P.H. Drenth & Jörn M. Schattenberg (2020) The nonalcoholic steatohepatitis (NASH) drug development graveyard: established hurdles and planning for future success, Expert Opinion on Investigational Drugs, 29:12, 1365-1375

Monitoring Response to treatment

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A treatment response biomarker

- ✓ should be linked to the disease pathway
- ✓ reflect target engagement of drug based on its mechanism of action
- ✓ or reflect improvement in underlying biology of the disease

Blood	Imaging	Combination
➢ ALT	✓ MRI-PDFF	✓ FAST
➢ PRO-C3	✓ VCTE	✓ MAST
➢ ELF	✓ cT1	✓ MEFIB
		✓ MASEF

Sanyal et al 2023 Clinical Gastroenterology and Hepatology Vol. 21, Iss. 8

DISEASE AND THERAPY MONITORING BIOMARKERS

Blood

alanine aminotransferase (ALT) - most widely used and known

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Absolute changes Evidence from obeticholic acid @18m

ALT

Trial

Name	***FLINT***
Duration	72 weeks
Analysis	final
Size	N=283
Phase	2
NCT	01265498

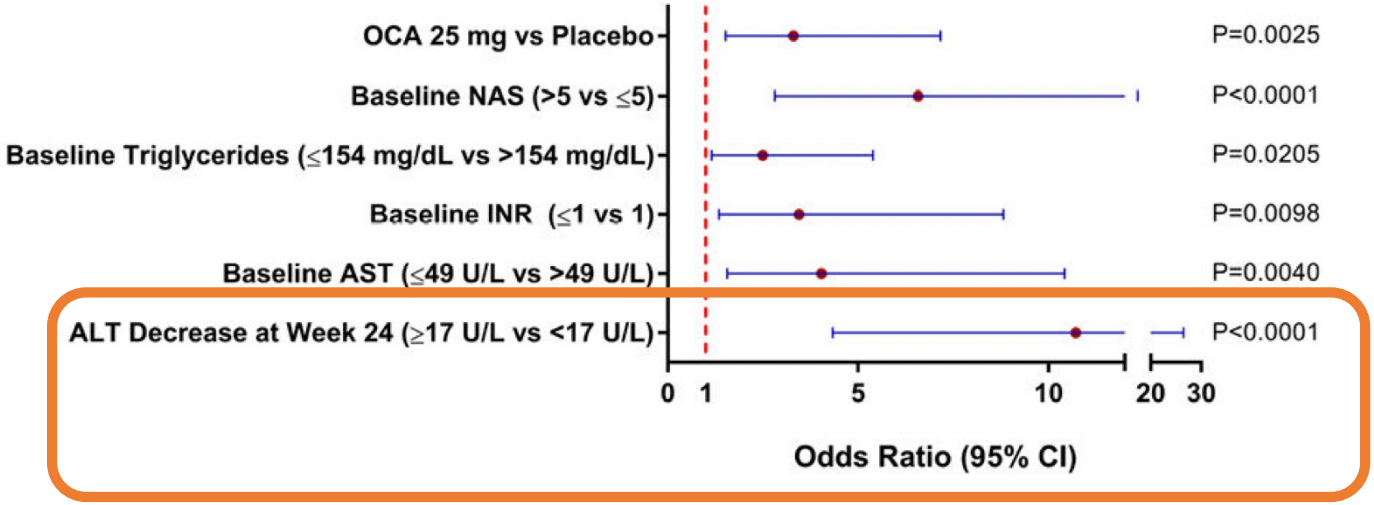


Figure 1. Forest Plot of Predictors of Histologic Response.
Plot shows the odds ratio and 95% CI for each of the selected predictors of responses, if the odds ratio is >1, the predictor is associated with higher odds of histological response. Significance of each of the selected predictors was assessed using a Wald Chi-Square test.

17 IU/L ALT decline was significantly associated with histologic markers of response

Loomba R et al. *Gastroenterology* 156,1 (2019): 88-95.e5.

alanine aminotransferase (ALT)

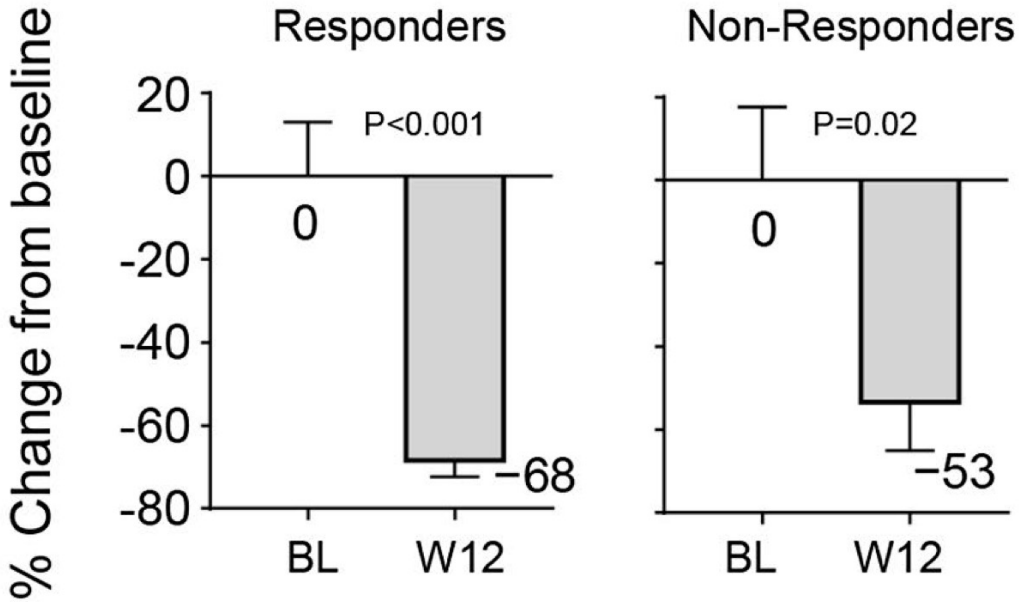
Relative changes Evidence from Aldafermin (FGF 19 analogue)

N=43; paired liver biopsies treated with s.c. NGM282 (1 m & 3 mg) once daily

ALT

Trial

Name	**NGM282 study**
Duration	12 weeks
Analysis	final
Size	N=43
Phase	2; open label
NCT	02443116

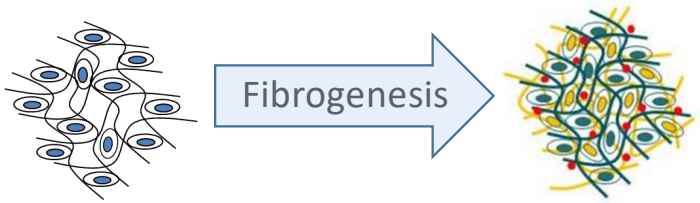


Responders: ≥ 2 pt improvement in NAS without worsening of fibrosis or improvement in ≥ 1 stage fibrosis without worsening of NASH

Harrison SA et al. Hepatology 2020;71:1198-1212.

Direct fibrogenesis marker

Diagnostic markers



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ELF

	AUROC ≥ F4	P vs FIB4	Youdin C/O	Sens	Spec
ELF	0.855	<0.001	10.1	82.1	73.3
NIS-4	0.725	1		78.1	61.4
Pro-C3	0.728	1.0	≥21.1	66.2	68.5
FM-VCTE	0.897	0.002	≥0.6	94.2	70.4

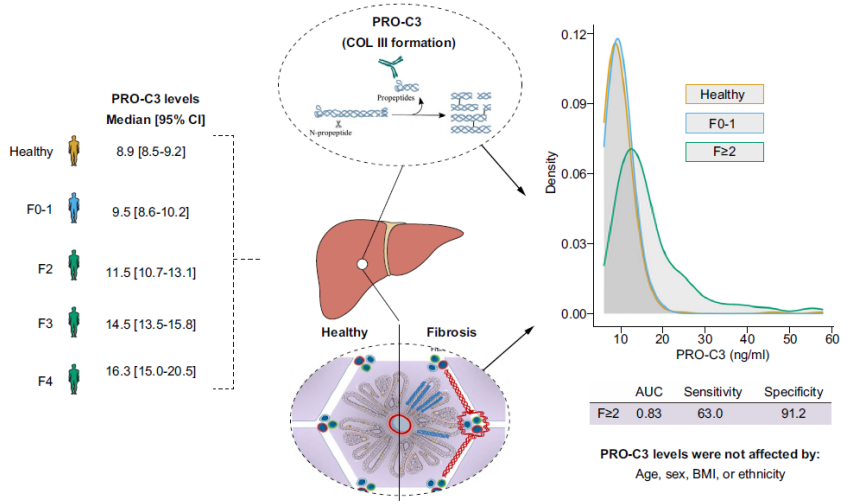
NIMBLE
Non-Invasive BioMarkers of MetaBolic Liver DiseasE

Sanyal A et al. AASLD 2021

Score 7.7 rules out fibrosis (Sn: 97%; Sp: 33%)	**Score 9.8** predicts fibrosis (Sn: 69%; Sp: 98%)	**Score 11.3** predicts cirrhosis (Sn: 83%; Sp: 97%)

Lichtinghagen R, et al. J Hepatol. 2013;59:236-242; Fagan KJ, et al. Liver Int. 2015;35:1673-1681.

PRO-C3



Erhardtsen, E. et al. JHEP Reports 3, 100317, (2021).

Relative change of collagen biomarker

Evidence from Aldafermin (FGF19 analogue)

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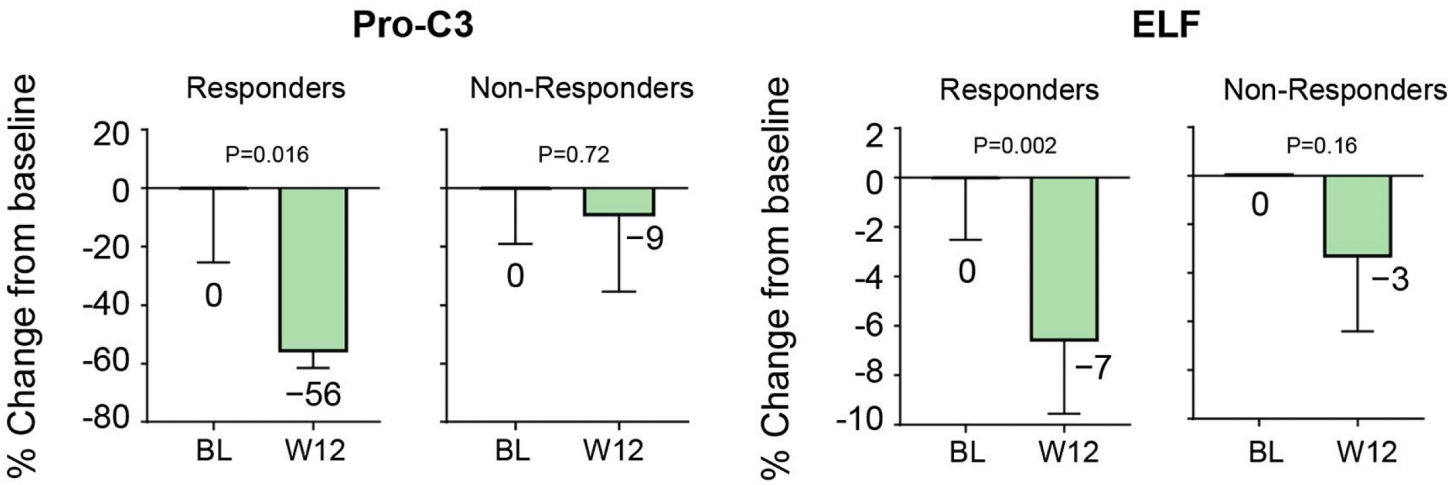
Pro-C3
ELF

N=43; paired liver biopsies treated with s.c. NGM282 (1 m & 3mg) once daily

Trial

Name	NGM282 study
Duration	12 weeks
Analysis	final
Size	N=43
Phase	2; open label
NCT	02443116



Responders: ≥ 2 pt improvement in NAS without worsening of fibrosis or improvement in ≥ 1 stage fibrosis without worsening of NASH

Harrison SA et al. Hepatology 2020;71:1198-1212.

Absolute Changes of PRO-C3

Evidence from Cenicriviroc (antagonist CCR2/5)

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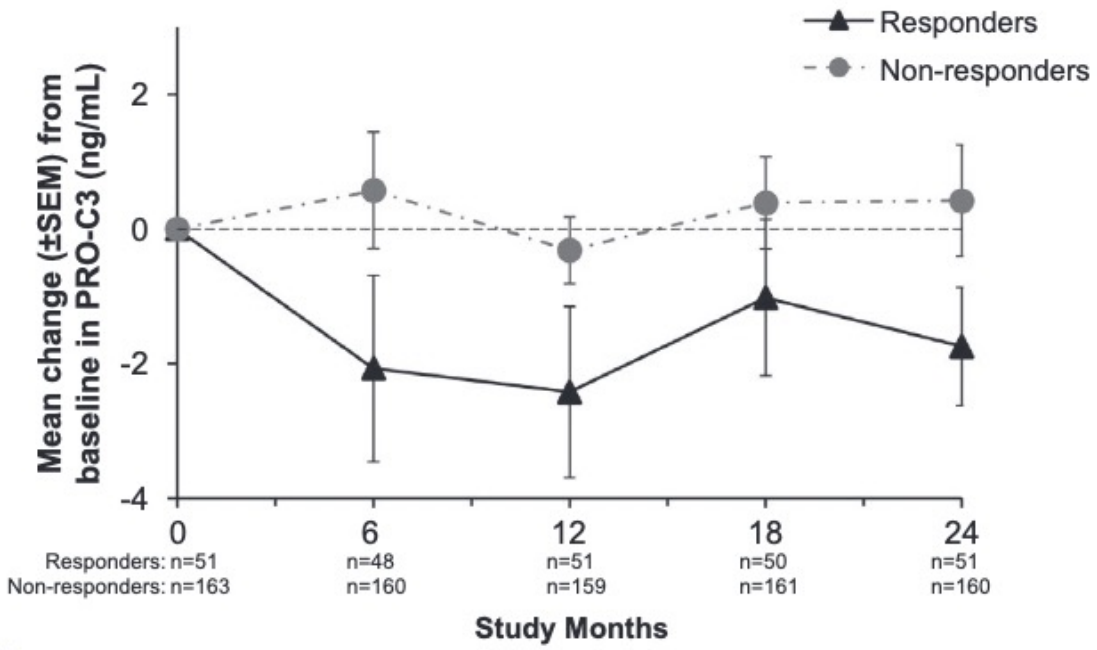
n= 289, up-to three paired biopsy with 150 mg CVC or placebo over 2 years

Pro-C3

Baseline ProC3 for both group: 14.3 ng/mL

Trial

Name	CENTAUER study
Duration	2 years
Analysis	final
Size	N=289
Phase	2b
NCT	02217475



Responders: ≥1-stage fibrosis

Ratziu V et al.. Hepatology. 2020 Sep;72(3):892-905

Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH

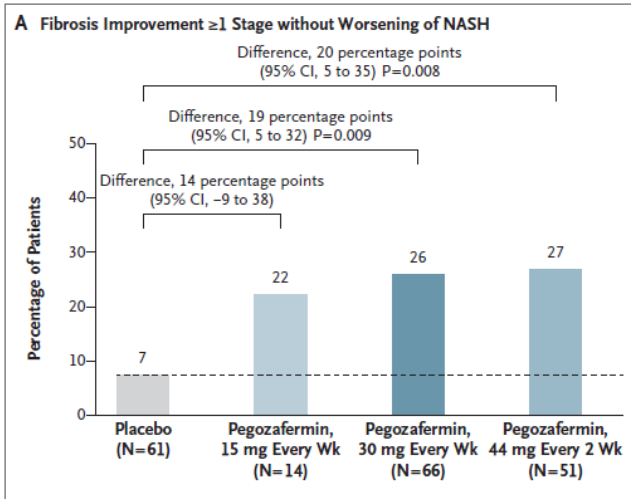


Table 2. Changes from Baseline to Week 24 in Selected Liver and Metabolic End Points (Full Analysis Population).*

End Point	Placebo (N=61)	Pegozafermin, 15 mg Weekly (N=14)	Pegozafermin, 30 mg Weekly (N=66)	Pegozafermin, 44 mg Every 2 Wk (N=51)
Alanine aminotransferase				
Absolute change — U/liter	−8.8±2.5	−24.3±5.1	−26.3±2.4	−23.5±2.7
Percentage change	−4.6±5.0	−37.7±10.1	−41.6±4.8	−31.8±5.4
Liver fat content†				
Absolute change — percentage points	−1.5±0.7	−4.6±1.4	−8.1±0.7	−8.2±0.8
Percentage change	−5.0±5.2	−27.1±10.3	−48.2±5.1	−41.9±5.6
Enhanced Liver Fibrosis test score‡	0.2±0.1	−0.3±0.1	−0.3±0.1	−0.3±0.1
Liver stiffness — kPa§	0.8±0.8	−1.4±1.5	−3.1±0.8	−2.4±0.9
Pro-C3				
Absolute change — ng/ml	−1.2±1.8	−9.9±3.7	−13.8±1.8	−11.4±2.0
Percentage change	6.4±4.1	−5.4±8.3	−18.1±4.0	−17.3±4.4
Iron-corrected T1 — msec†	−6.1±11.7	−46.7±21.3	−92.4±10.7	−69.8±12.3
Liver volume				
Absolute change — ml	−62±38	−127±78	−304±37	−241±42
[illegible]		−5.9±3.1	−12.5±1.5	−9.5±1.7

NASH CRN fibrosis stage — no. (%)§					
F1	2 (3)	3 (14)	2 (3)	0	7 (3)
F2	20 (28)	6 (29)	21 (29)	21 (37)	68 (31)
F3	47 (66)	9 (43)	47 (64)	30 (53)	133 (60)
F4	2 (3)	3 (14)	3 (4)	6 (11)	14 (6)
NAFLD activity score¶	5.0±1.2	4.8±1.2	5.3±1.1	5.2±1.0	5.1±1.1
Liver fat content — %‖	16.7±7.1	15.8±6.4	16.7±7.0	15.8±7.8	16.4±7.2
Liver stiffness — kPa**	14.1±7.7	11.2±2.9	12.5±4.2	13.2±10.3	13.0±7.3
Pro-C3 — ng/ml††	49.8±17.5	61.6±30.7	53.6±22.3	52.3±18.8	52.8±21.1

	−23±12	−37±6	−19±7
	−6.1±3.5	−9.8±1.7	−5.2±1.9
	1.1±0.7	1.1±0.3	1.2±0.4
	20.6±11.9	30.0±5.6	27.7±6.1
9.0)	−8.3 (−26.8 to 10.3)	−40.5 (−73.0 to −7.0)	−14.0 (−45.5 to 7.0)
3.6)	−5.9 (−22.9 to 6.4)	−26.6 (−39.7 to −5.8)	−10.1 (−28.6 to 3.5)
	−0.1±0.2	−0.3±0.1	−0.2±0.1

DISEASE AND THERAPY MONITORING BIOMARKERS

Imaging

Liver fat content and NASH resolution

Evidence from Ph2 Resmetirom (THRbeta agonist)

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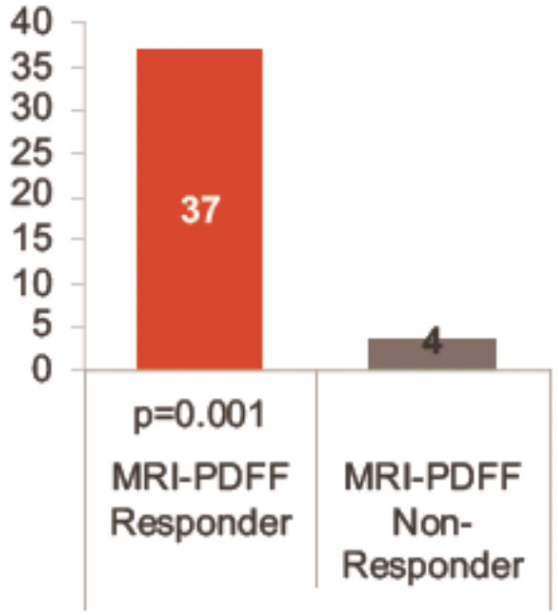
MRI Responders: ≥ 30% relative decline in LFC

MRI-PDFF

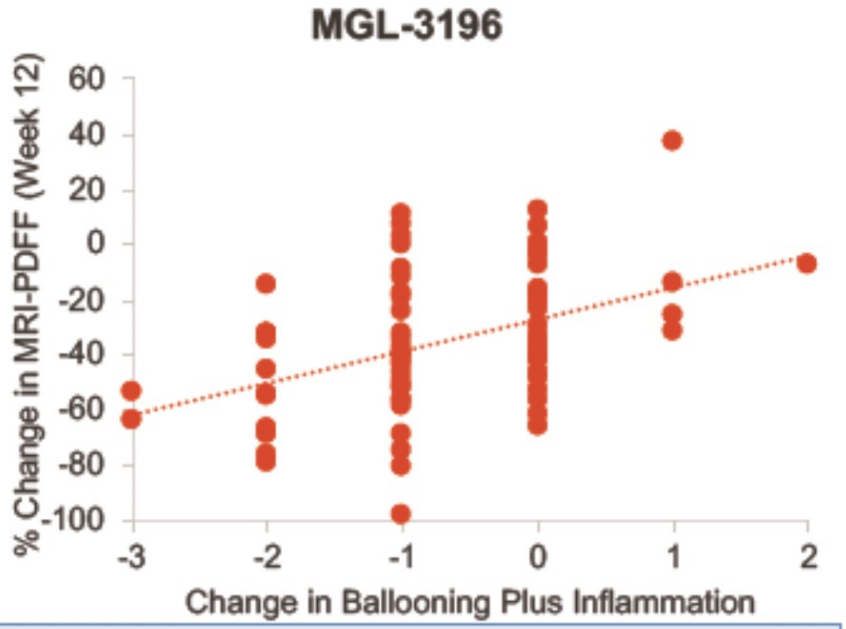
Trial

Duration	36 weeks
Analysis	final
Size	N=125
Phase	2
NCT	02912260

NASH Resolution (%)
MGL-3196-treated



MRI-PDFF Week 12, % Relative Change: Correlation with Change in Ballooning Plus Inflammation Scores



Harrison SA et al. Hepatology 2018;68:9A-10A.

Benefit of ≥30% relative decline in MRI-PDFF

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MRI-PDFF

Change in MRI-PDFF and Histologic Response in Patients with NASH: A Systematic Review and Meta-Analysis – 7 studies / 346 patients

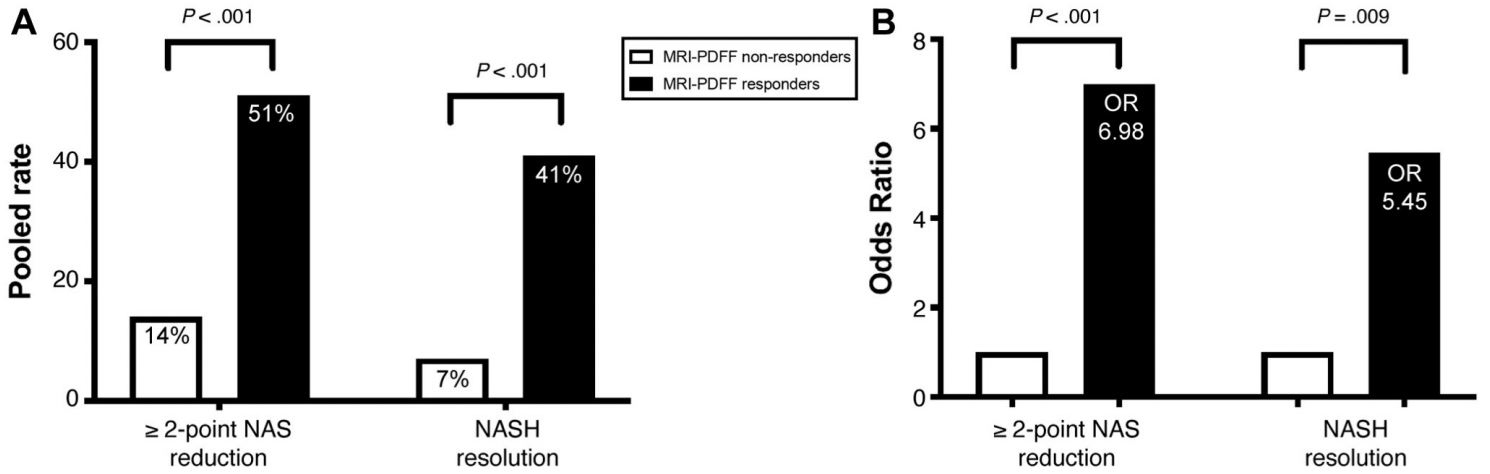

Figure 3. (*A*) The rate of 2-point improvement in NAS in MRI-PDFF responders vs nonresponders was 51% vs 15% ($P < .001$), and the rate of NASH resolution in MRI-PDFF responders vs nonresponders was 41% vs 7% ($P < .001$). (*B*) The odds of 2-point improvement in NAS in MRI-PDFF responders vs nonresponders was 6.98 (95% CI, 2.38–20.43; $P < .001$), and the odds of NASH resolution in MRI-PDFF responders vs nonresponders was 5.45 (95% CI, 1.53–19.46; $P < .009$).

"These results support the use of MRI- PDFF in non-invasive monitoring of treatment response in early-phase NASH clinical trials"

Stine JG et al. Clin Gastroenterol Hepatol. 2021 Nov;19(11):2274-2283.e5.

Assessment of cT1 - aiming for fibroinflammation

data from obeticholic acid

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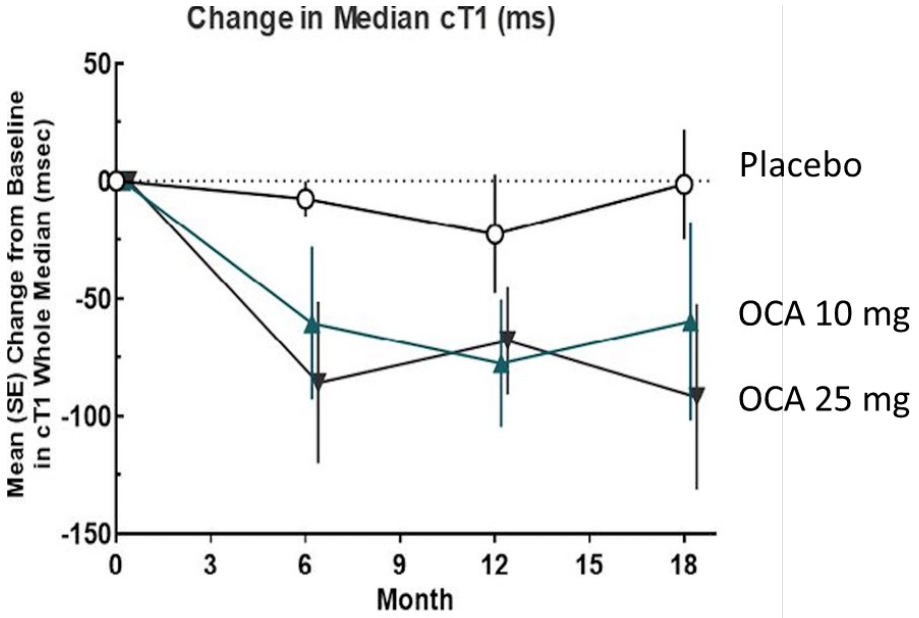
Corrected T1 (cT1) is an MRI-based diagnostic imaging biomarker intended to be used as a proxy for inflammation and fibrosis in NASH

cT1

Trial

Name	Regenerate
Duration	18 month
Analysis	interim
Size	931
Phase	3
NCT	NCT02548351



Baseline cT1

Placebo: 856.7 ms

OCA 10 mg: 943.2 ms

OCA 25 mg: 882.1 ms

Following 18 months of treatment, a dose-dependent reduction in mean cT1 from baseline was observed (placebo: -1.4 ms; OCA 10 mg: -59.6 ms; OCA 25 mg: -91.7 ms)

Anstee Q, et al. Gut 2020;**69:**A17.

Assessment of Liver stiffness with VCTE

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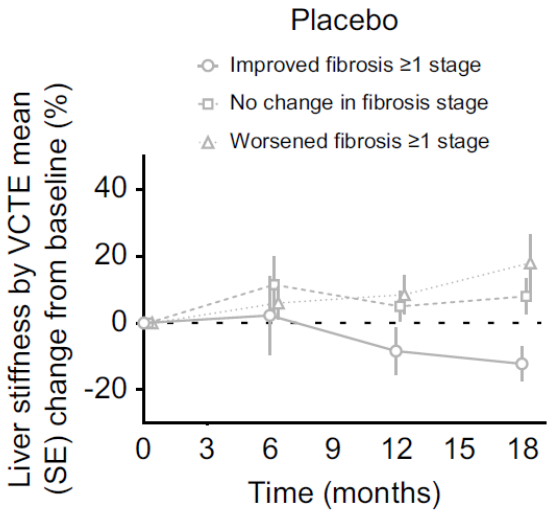
Change from baseline by treatment group and histological fibrosis change

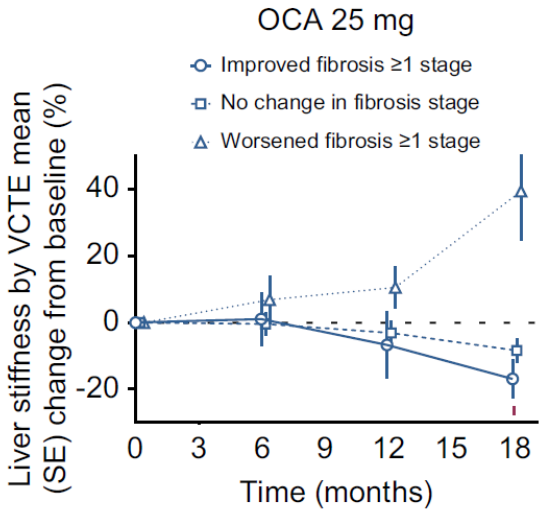
VCTE

Trial

Name	Regenerate
Duration	18 month
Analysis	interim
Size	931
Phase	3
NCT	NCT02548351



Improved, n =	40	38	38	37
No change, n =	111	100	104	100
Worsened, n =	42	41	40	39



Improved, n =	66	63	59	57
No change, n =	92	90	87	82
Worsened, n =	26	25	26	25

- **Changes correlate with fibrosis stage**
- **Stable fibrosis, LSM improved with OCA 25 mg vs PBO**

Rinella J Hepatology 2022;76:536-48.

Changes in liver stiffness (VCTE)

evidence from the MAESTRO NASH study (resmetirom)

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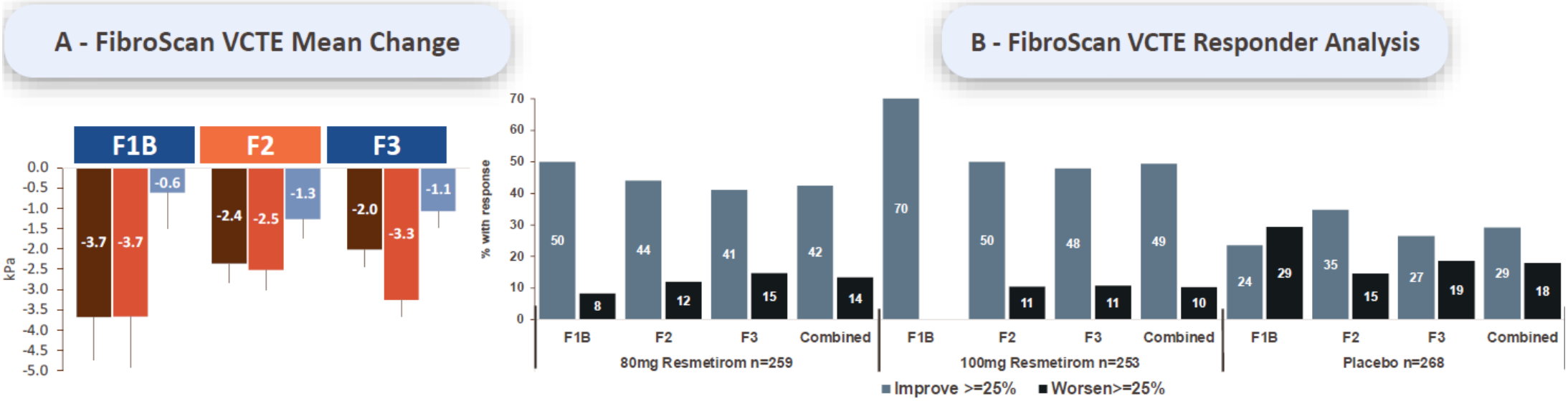

Effect size depending on disease stage

Madrigal

Harrison S et al. Presented at the EASL Congress 2023; Vienna

Dynamics of NIT change?

Different value of changes at different time points

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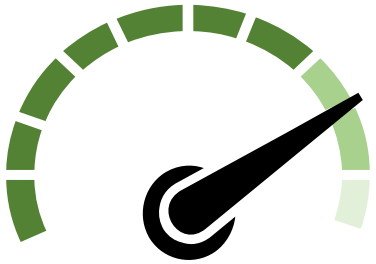
Early Change

< 12 weeks after treatment initiation

Mid-range Change

12 - 24 weeks after treatment initiation

Late Change



> 24 weeks after treatment initiation

Future Considerations

"Religious truth is captive in a small number of little manuscripts which guard the common treasures, instead of expanding them.

Let us break the seal which binds these holy things; let us give wings to truth that it may fly with the Word, no longer prepared at vast expense, but multitudes everlastingly by a machine which never wearies to every soul which enters life."

— Johannes Gutenberg

NIT changes and treatment response

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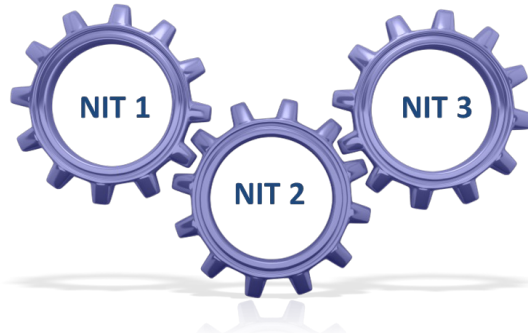
- Clearly NITs will be used to assess treatment response, but one size does not fit all
- therapeutic response monitoring – take mechanism and disease stage into account
- Combinations could reduce the noise to signal ratio - how many and which ones are needed?



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