2020 VIRTUAL GI AND LIVER SYMPOSIUM

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NAFLD/NASH Abstracts EASL/AASLD

Mazen Noureddin, MD, MHSc

Cedars Sinai Medical Center

Disclosures

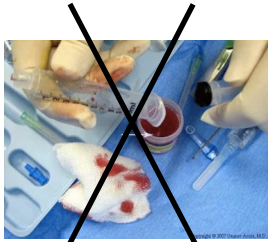
- **Faculty: Mazen Noureddin, MD, MHSc**
- MN has been on the **advisory board** for 89BIO, Gilead, Intercept, Pfizer, Novartis, Novo Nordisk, Allergan, Blade, EchoSens, Fractyl, Terns, OWL, Siemens, Roche diagnostic and Abbott; MN has **received research support** from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Shire, Viking and Zydus; MN is a **minor shareholder** or has stocks in Anaetos and Viking.

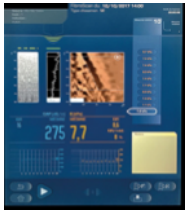
Objectives

- **Natural History**
- **Diagnostics**
- **Therapeutics**

Cirrhosis regression &others

Menu of Options





Many successful stories

Objectives

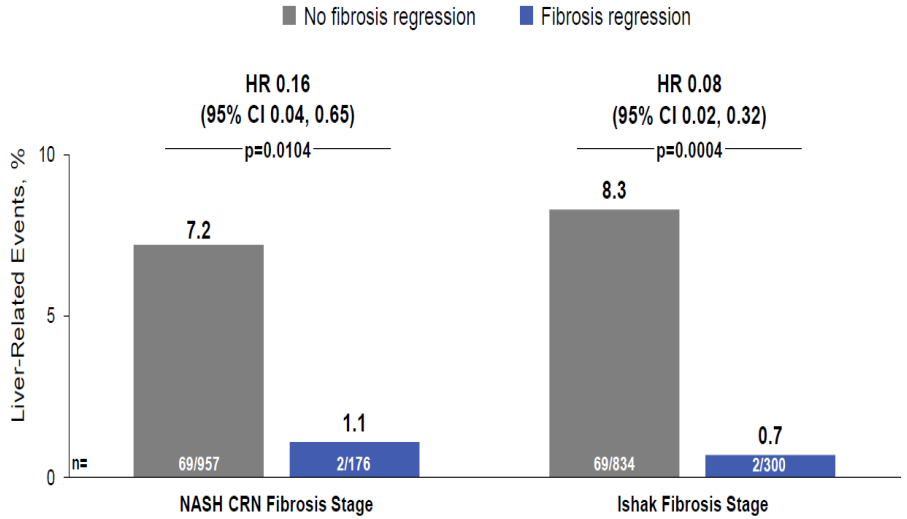
- **Natural History**

Cirrhosis regression &others

Cirrhosis Regression is Associated with Improved Clinical Outcomes in Patients with Nonalcoholic Steatohepatitis. Sanyal AJ, et al. # 0090

- Associations between cirrhosis regression and NITs and clinical outcomes were assessed post-hoc in the Simtuzumab and Selonsertib clinical trials (>1000 Child's A NASH Cirrhotics)

Fibrosis Regression is Associated with Reduction in Events in Patients with Cirrhosis

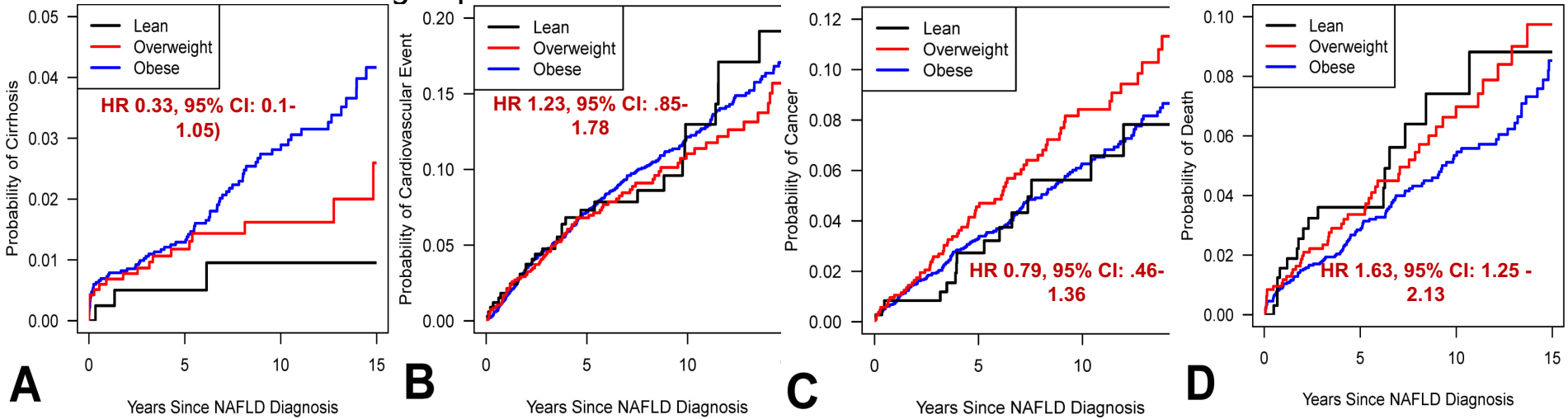


♦ Cirrhosis regression observed in 16% (176/1135) of patients over 48 weeks

- Patients with cirrhosis regression had milder disease at baseline (e.g., hepatic collagen, FIB-4, LSM, platelets, and fibrosis stage)
- Patients with cirrhosis regression had greater reductions in ELF and LSM by transient elastography. Changes in NFS and FIB4 or platelets were not significantly associated with cirrhosis regression
- Data support the utility of histological fibrosis regression and NITs (ELF and LSM) as efficacy surrogates in NASH cirrhosis clinical trials.

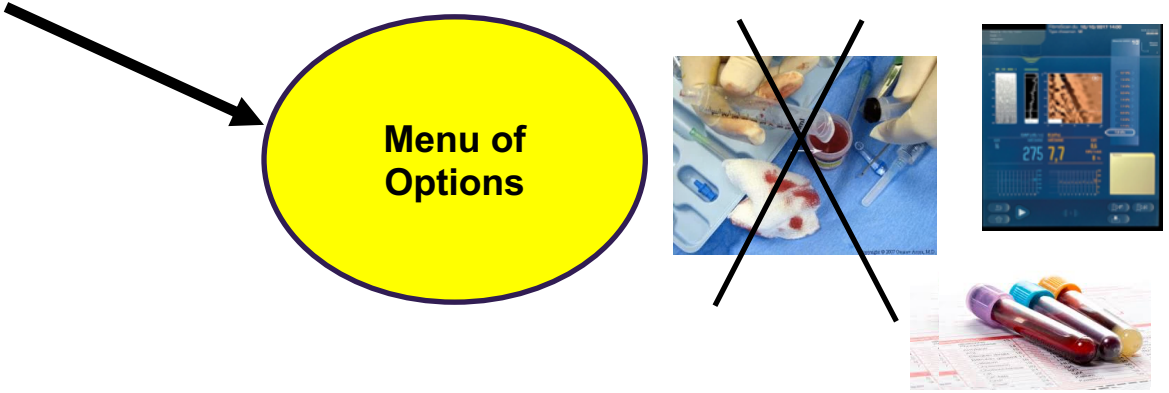
The Natural History of Lean Nonalcoholic Fatty Liver Disease: a Longitudinal US Population Study. Ahmed OT, et al. Oral presentation # 0086

- Natural history of lean, overweight, and obese NAFLD in Olmsted county, MN with 20-years follow-up
- Final NAFLD cohort = 4,843. Lean = 414, Overweight = 1,189, and Obese = 3,231
- Individuals with lean NAFLD may have lower risk for incident cirrhosis, but no differences in the incidences of cardiovascular events or cancer. Inexplicably, their mortality was significantly higher than obese NAFLD group.



Objectives

- **Diagnostics**



FDA: Liver Histologic Improvement Endpoints Likely to Predict Clinical Benefit

NASH Resolution

- **Resolution of steatohepatitis and**
- **No worsening of liver fibrosis**

Fibrosis Improvement

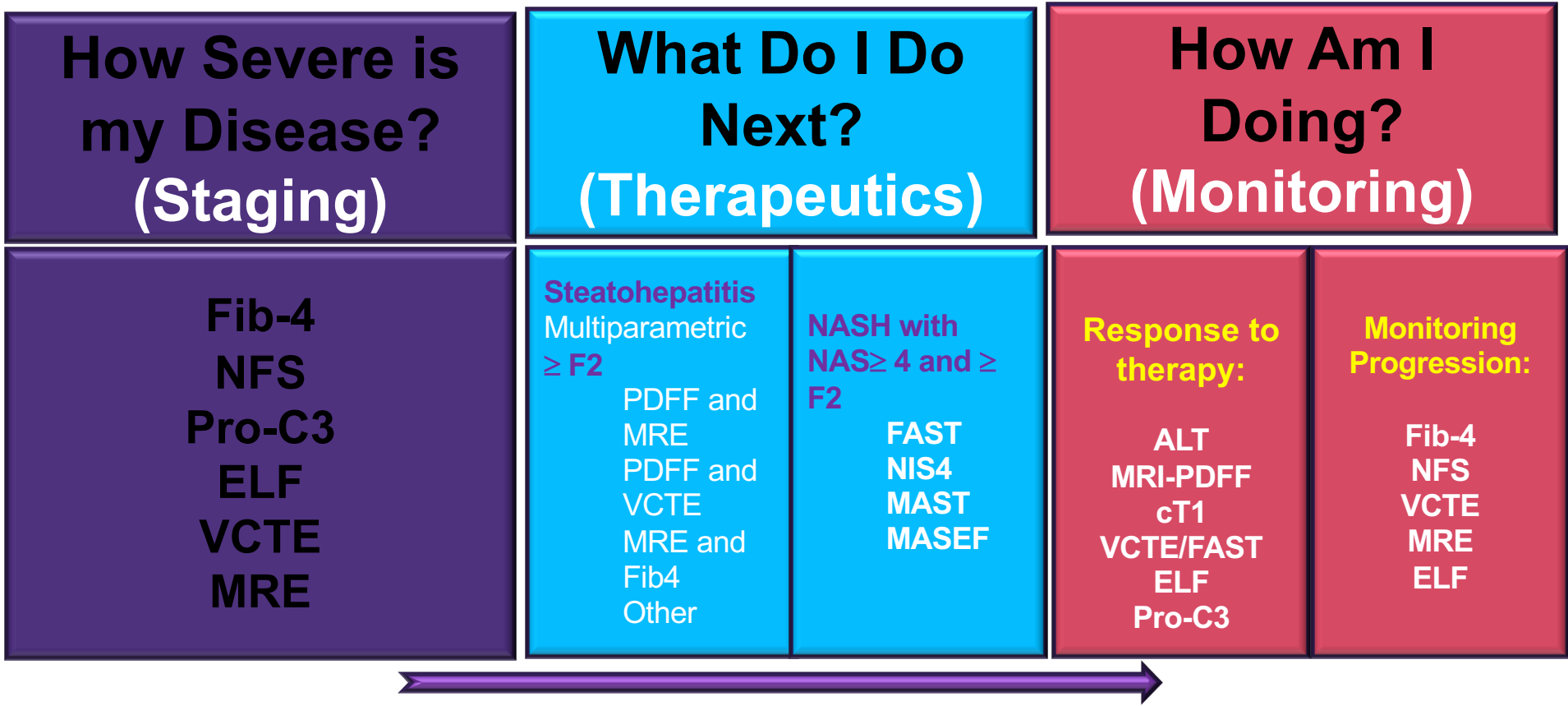
- Improvement ≥ 1 fibrosis stage

and

- **No worsening of steatohepatitis**

US FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

NITs, NAFLD SIG, Noureddin



MRE and FIB-4 for ruling in ≥stage 2 fibrosis

UCSD-NAFLD Cohort
(N=238)

MRE ≥ 3.3kPa
PPV: 86.9

+

FIB-4 ≥ 1.6
PPV: 61.5

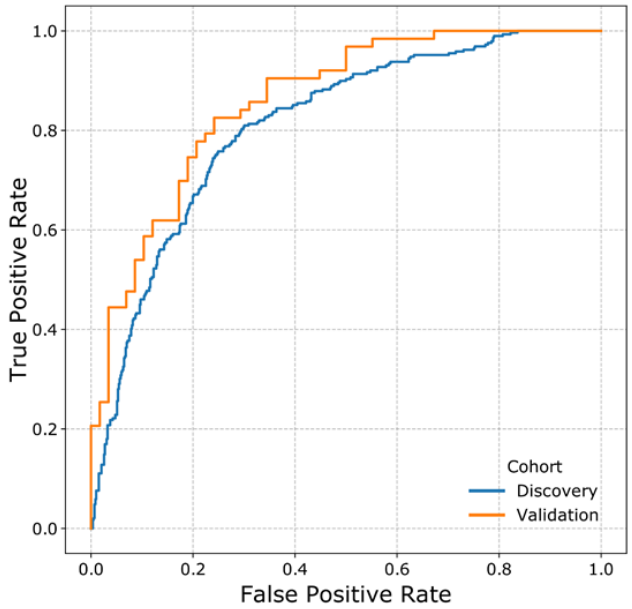
MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 97.1

Japan-NAFLD Cohort
(N=222)

MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 91.0

Jung J et al; EASL 2020

MASEF: For NASH with NAS≥ 4 and ≥ F2

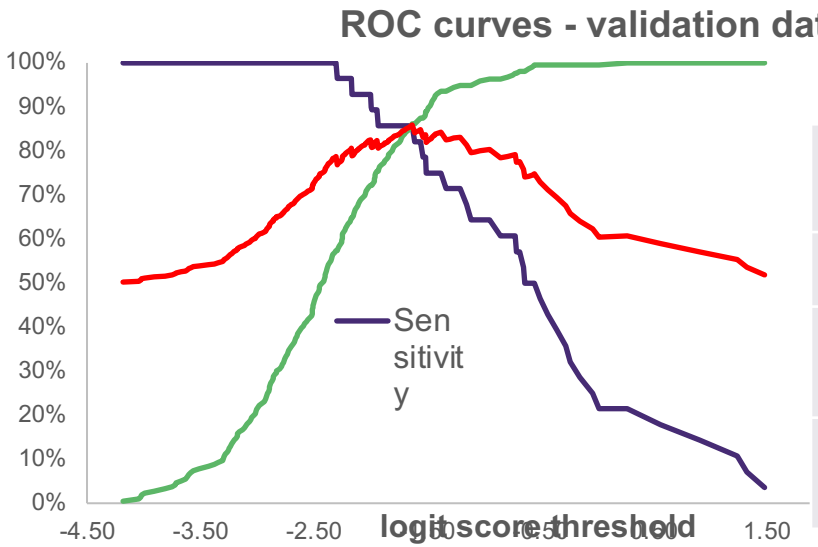


- The serum-based Metabolomics Advanced Steatohepatits Fibrosis Score (MASEF) for the non-invasive identification of patients with NASH and significant fibrosis
- The final MASEF score included only12 lipids, body mass index (BMI), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

ROC ANALYSIS					
Cohort	**AUC**	**sens**	**spec**	**PPV**	**NPV**
Discovery	0.81	0.36	0.96	0.86	0.62
Validation	0.82	0.20	0.95	0.62	0.75

Noureddin….Sanyal et al, EASL 2020
Noureddin…..Sanyal et al, AASLD 2020

MAST: For NASH with NAS≥ 4 and ≥ F2



MRI-PDFF + MRE +AST

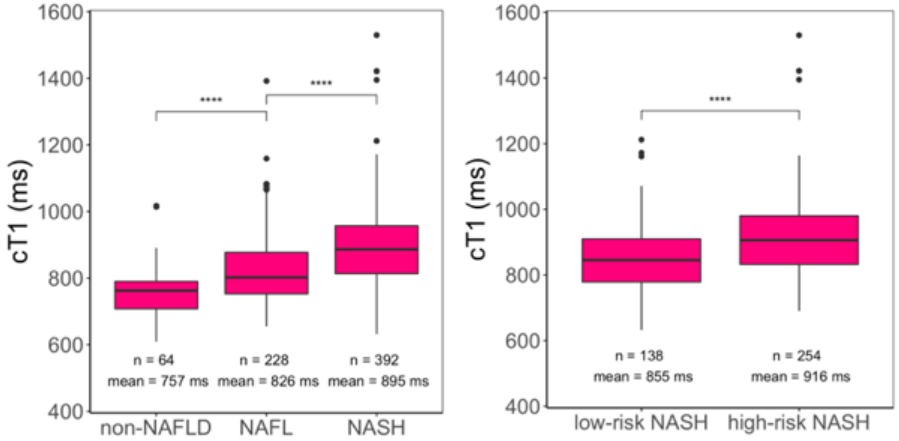
	AUCROC (95% CI)	Rule-out zone			Rule-in zone		
		Sensitivity	Specificity	NPV	Sensitivity	Specificity	PPV
Derivation	0.943 (0.901-0.984)	89.3%	73.6%	98.3%	82.1%	90.3%	51.6%
Validation	0.860 (0.781-0.939)	88.9%	63.5%	96.8%	50.0%	90.6%	51.4%

Noureddin, Harrison, Alkhouri; AASLD 2020

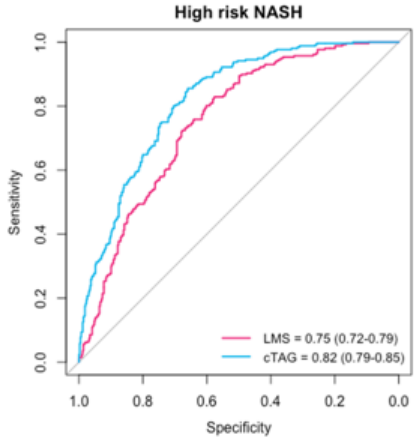
Diagnostic accuracy of MRI Biomarkers cT1 and fat for high-risk nonalcoholic steatohepatitis. Dennis A, et al. Oral # 0089

cT1 with AST and fasting glucose could accurately identify NASH patients with fibrosis

cT1 distinguishes different stages of the disease spectrum.



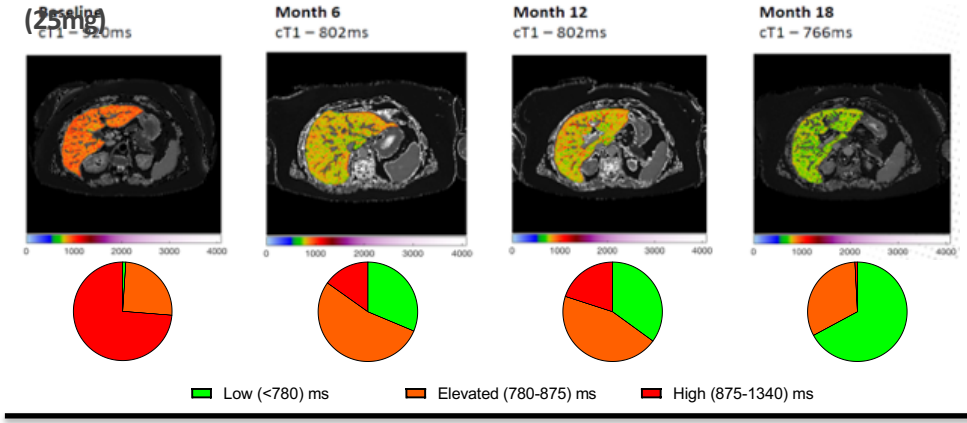
ROC curves for LiverMultiScan (cT1 + PDFF), AUROC(CI) = 0.75 (0.72–0.79) and cTAG (cT1 + AST + glucose), AUROC(CI) = 0.82 (0.79 – 0.85) to diagnose high risk NASH as defined by NAS≥4 and F≥2.

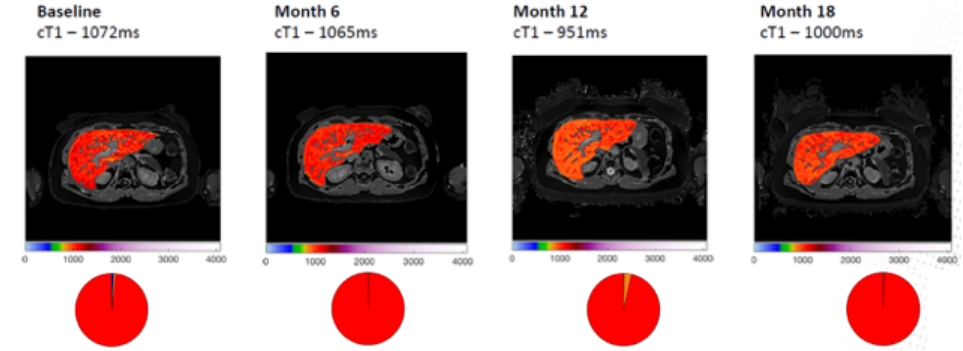


Poster # 1495: Liver *Multiscan*™ was the most cost-effective diagnostic pathway for detecting high-risk NASH patients, compared to MRE or VCTE based strategies, over a broad range of prices.

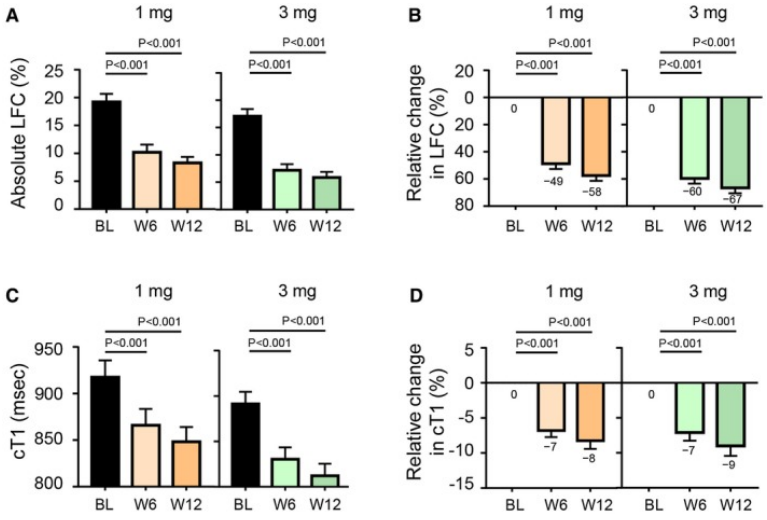
LiverMultiScan : Measuring response

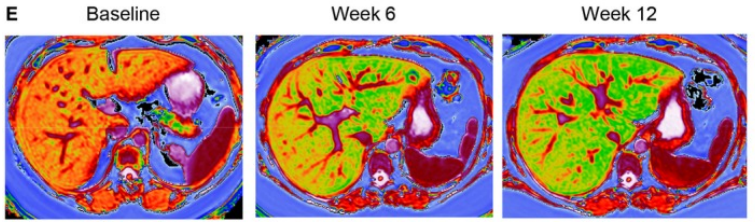
OCA





NGM-282

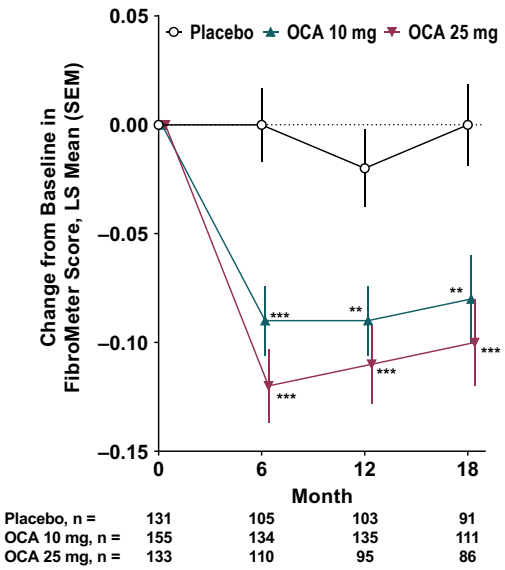


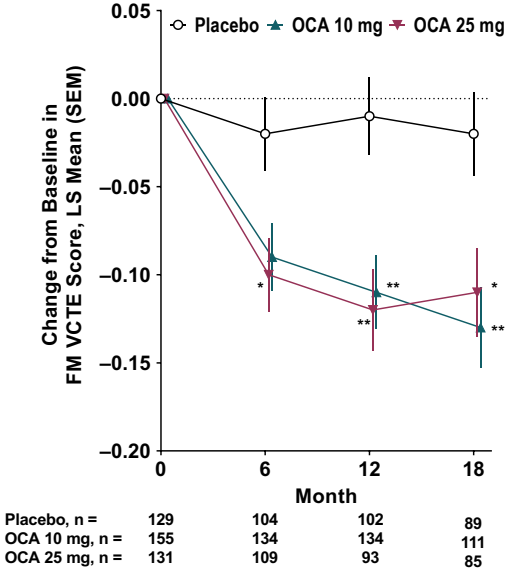


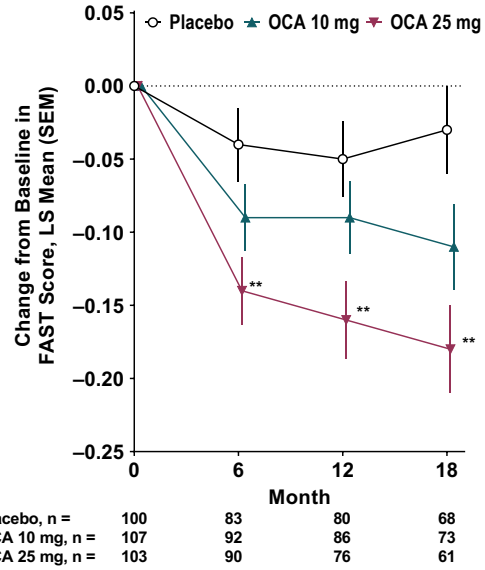
Harrison et al. Hepatology, 2020
Loomba et al. EASL 2020.

FibroMeter, FibroMeter VCTE, and FAST Scores Over Time (ITT Population[a]): REGENRATE Study

- At Month 6, OCA-treated patients experienced improvements in FibroMeter, FibroMeter VCTE, and FAST
  - Improvements were sustained through Month 18 (except FAST score with OCA 10 mg)

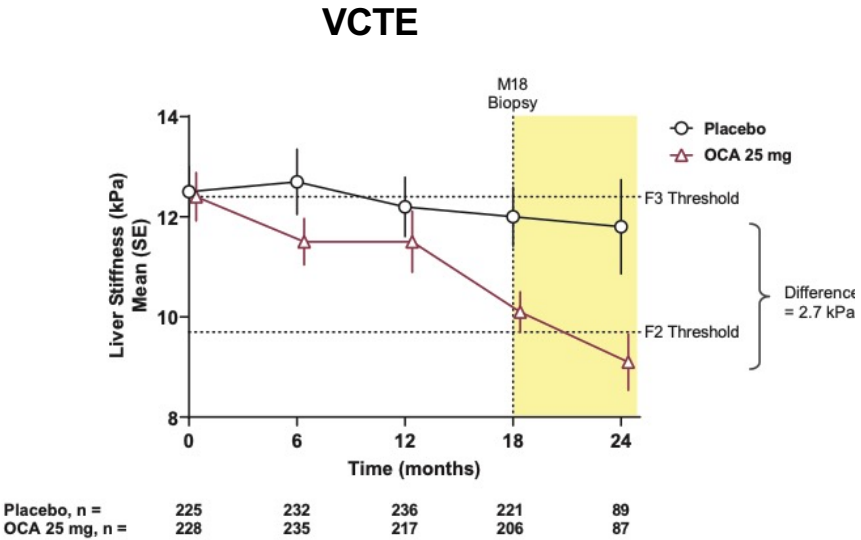


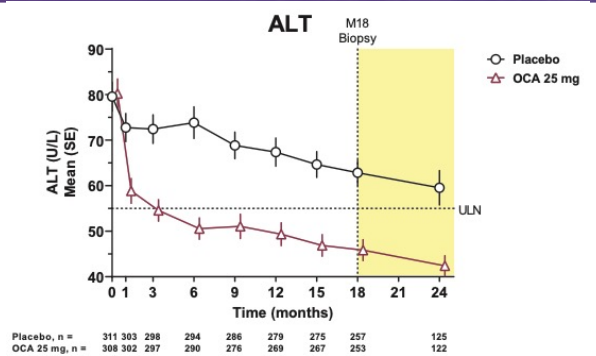


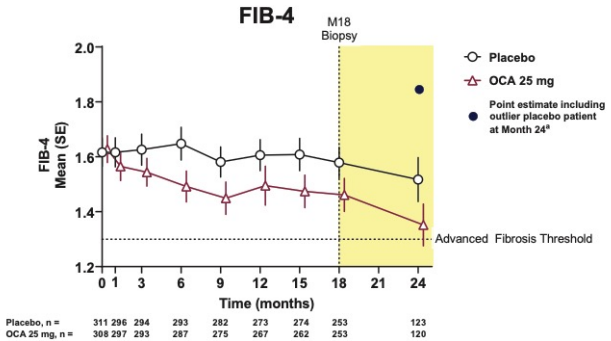


Borusier,..Ratziu; EASL 2020

ALT, VCTE, and FIB-4 Score Over Time (ITT Population[a])



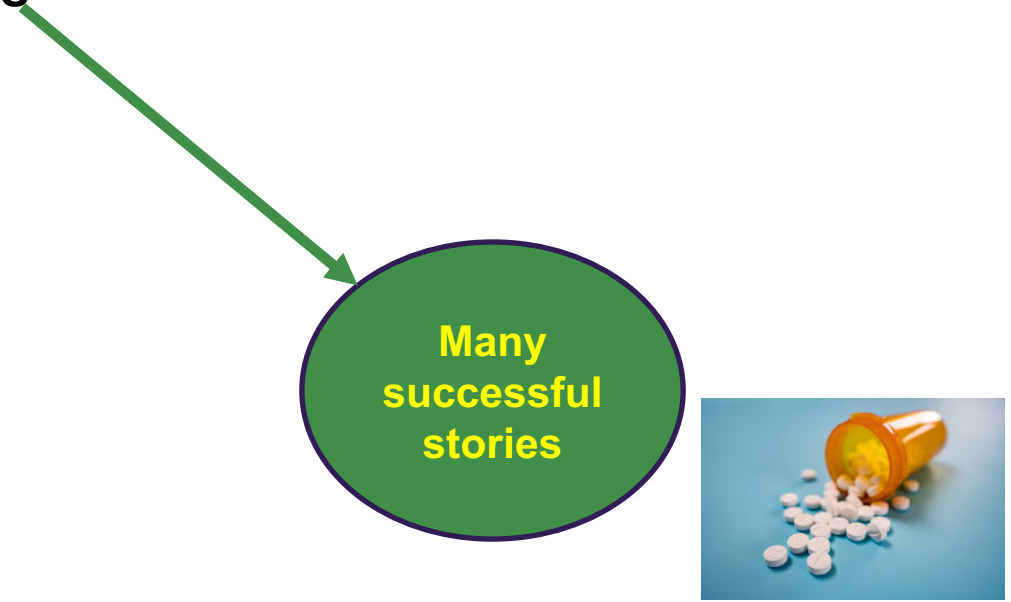




Loomba….Noureddin: EASL 2020

Objectives

- **Therapeutics**



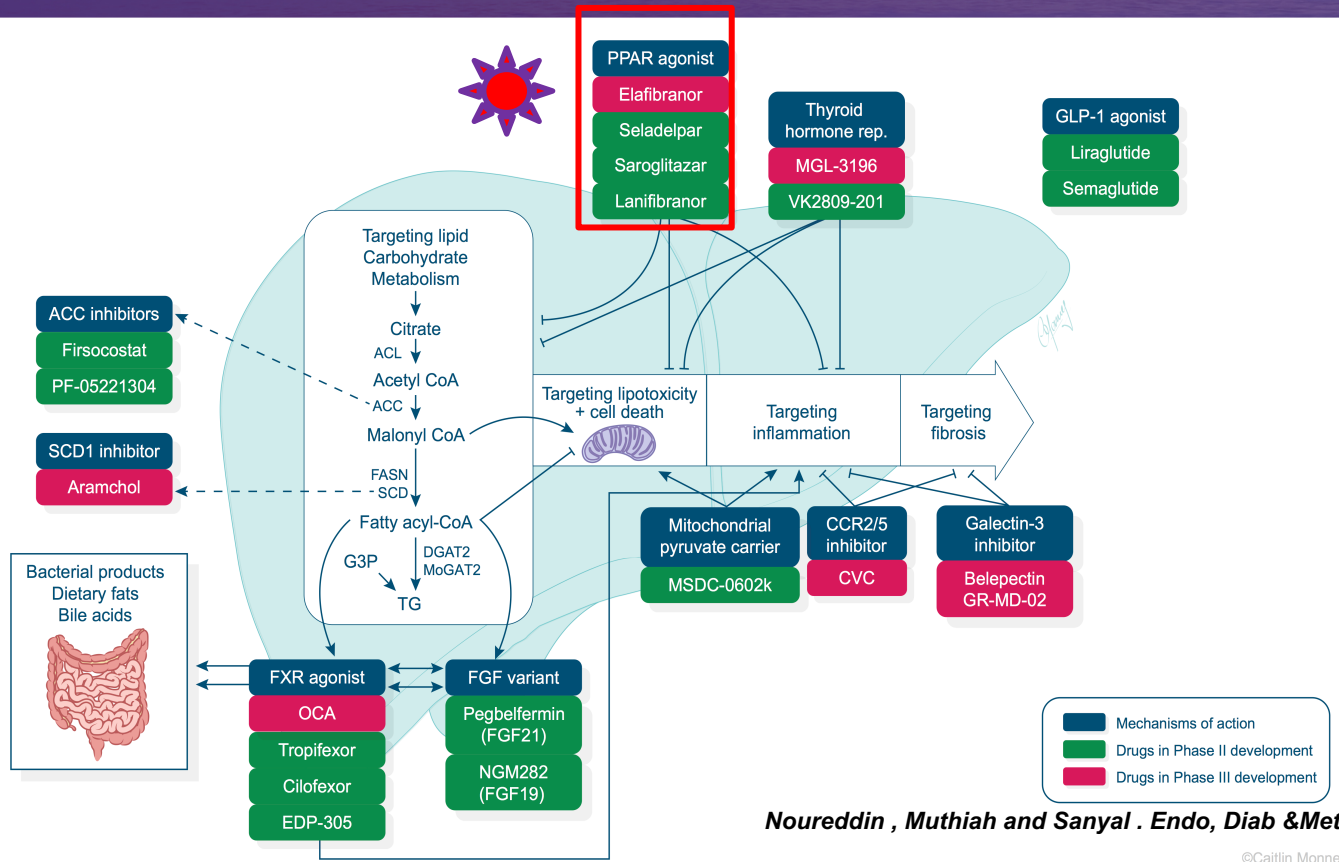
TREATMENT TRIALS

- Histological Endpoints

1. Lanifibranor (# 0012)
2. Semaglutide (# 0010)
3. NGM282 (# 0072)
4. Tropifexor (# 0139)
5. Elafibranor (# LP 23)
6. Seldalapar (# 1710)

- POC & Phase 2A Studies

1. Efruxiferin (# 0008)
2. FASN inhibitor (# 0067)
3. A3 Adenosine receptor Antagonist (# L01)
4. Sema + cilofexor + firsocostat (# L02)



Noureddin , Muthiah and Sanyal . Endo, Diab &Meta 2019

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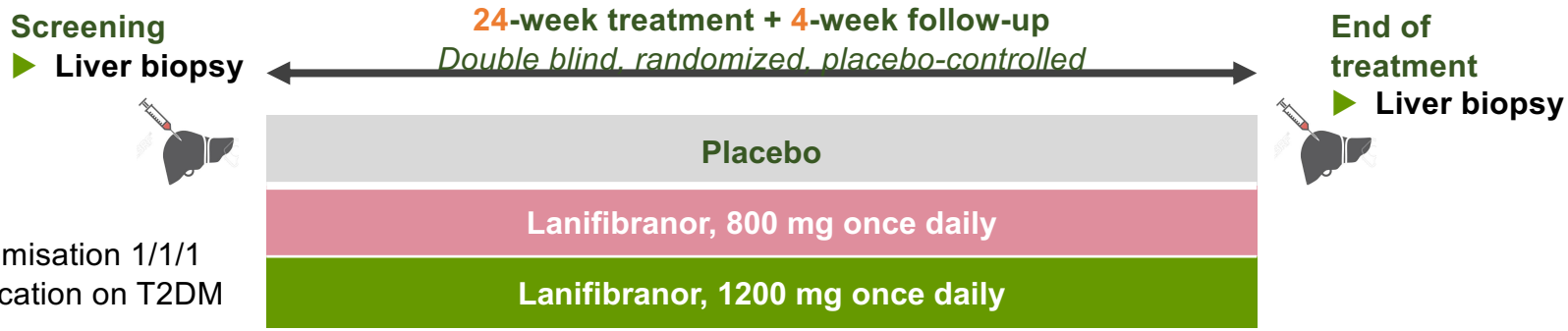
The panPPAR agonist lanifibranor results in highly significant improvements in both resolution of NASH and regression of fibrosis at 24 weeks in non-cirrhotic NASH: results of the NATIVE Phase 2b trial

Francque S, Bedossa P, Ratziu V, Anstee Q, Bugianesi E, Sanyal A, Harrison S, Loomba R, Balabanska R, Mateva L, Lanthier N, Alkhouri N, Moreno C, Schattenberg J, Stefanova-Petrova D, Vonghia L, Rouzier R, Guillaume M, Huot Marchand P, Baudin M, Richard MP, Abitbol JL, Broqua P, Junien JL, Abdelmalek M

Abstract # 0012

Trial design

Clinicaltrials.gov identifier: NCT03008070

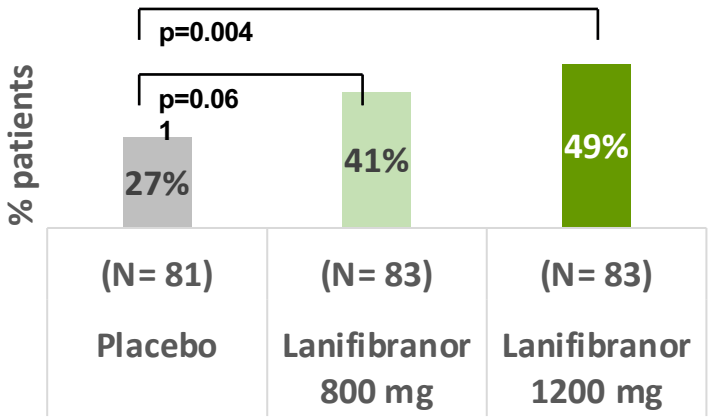


- **Main inclusion criteria**: patients with biopsy-proven NASH confirmed by central reader having Steatosis-Activity-Fibrosis (SAF) scores of 1-3 for **S**teatosis, 3-4 for **A**ctivity, and <4 for **F**ibrosis

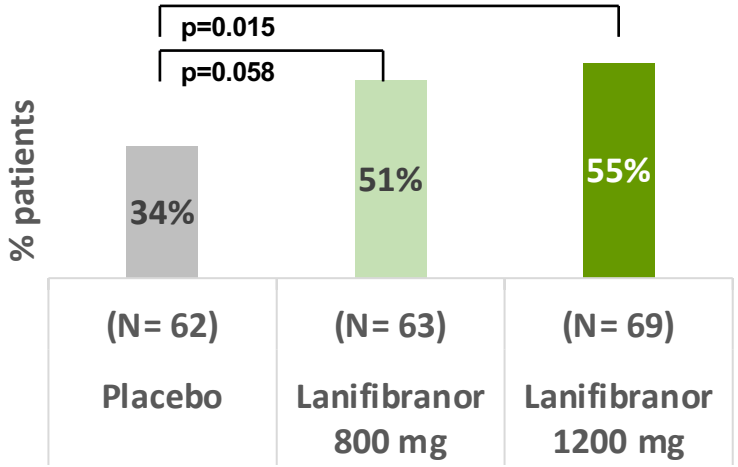
Patient population	# patients	Definition
Full Analysis Set (FAS) = Safety set	247	Patients randomized having received at least one dose of lanifibranor/placebo
Per Protocol (PP)	194	Patients with paired biopsies and without deviation impacting efficacy results

Reduction of 2 points of SAF Activity Score and no worsening of fibrosis

FAS (N = 247)*



PP (N = 194)



- **Lanifibranor 1200 mg met the primary endpoint in both FAS and PP populations**
- **Similar results in F2-F3 patients**
- **Consistent response in diabetic and non-diabetic patients**, See Poster LP9

P-values -values were calculated using Cochran Mantel Haenszel test to assess lanifibranor's effect versus placebo, stratified on T2DM status
** Missing biopsies are considered non-responders*

Main histological secondary endpoints

Statistically significant

Non- statistically significant

FAS (N=247)*

	Placebo (N = 81)	Lanifibranor 800 mg (N = 83)	Lanifibranor 1200 mg (N = 83)
Resolution of NASH and no worsening of fibrosis[1]	19%	0.043 33%	<0.001 45%
Improvement of fibrosis by at least one stage and no worsening of NASH[2]	24%	0.53 28%	0.011 42%
Resolution of NASH and improvement of fibrosis[3]	7%	0.017 21%	<0.001 31%

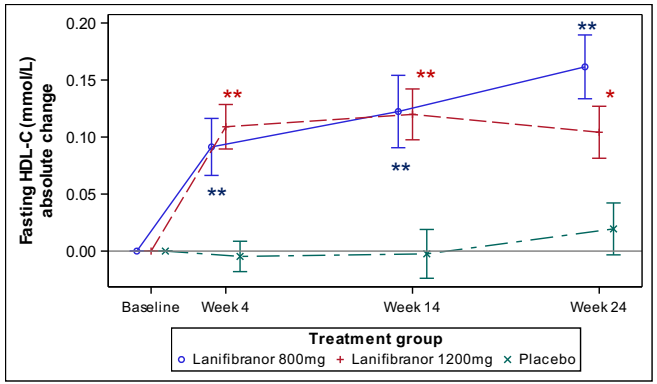
Similar results in the PP population, Consistent response in diabetic and non-diabetic patients, See Poster LP9

(1) Resolution of NASH with no worsening of fibrosis at week 24: NAS-I = 0 or 1 (NAS-Inflammation), NAS-B = 0 (NAS-Ballooning) and no worsening of NAS-F from baseline; (2) Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24; (3) Resolution of NASH and improvement of fibrosis at week 24: NAS-I = 0 or 1, NAS-B = 0 and an improvement of NAS-F ≥ 1 stage

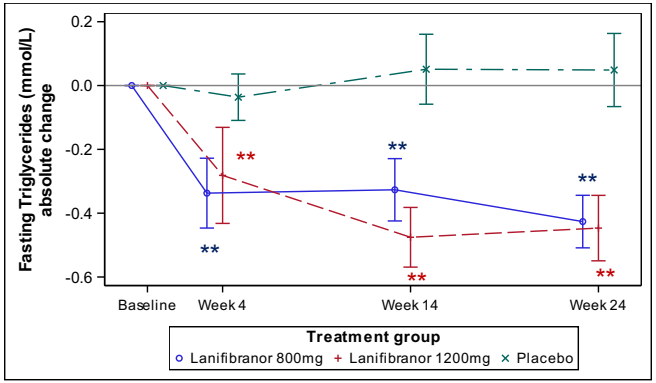
*P-values -values were calculated using Cochran Mantel Haenszel test to assess lanifibranor's effect versus placebo, stratified on T2DM status ; * Missing biopsies are considered non-responders*

Lipid profile

Absolute change from baseline in HDL-C



Absolute change from baseline in triglycerides



*** p<0.01 **p<0.001**

- **Statistically significant increase in HDL-C at 4 weeks**
- **Statistically significant decrease in triglycerides at 14 weeks**
- **No change in LDL-cholesterol**
- **Consistent results in diabetic and non-diabetic patients; See Poster LP9**

Glycemic control in T2DM patients

ACFB: Absolute change from baseline	Placebo N=35	Lanifibranor 800 mg N=33	p-value	Lanifibranor 1200 mg N=35	p-value
Fasting glucose (mmol/L)	0.28	-1.39	<0.001	-0.93	<0.001
Fasting insulin (pmol/L)	-40.2	-145.9	<0.001	-108.6	0.018
HbA1c (%)	0.08	-0.61	<0.001	-0.65	<0.001

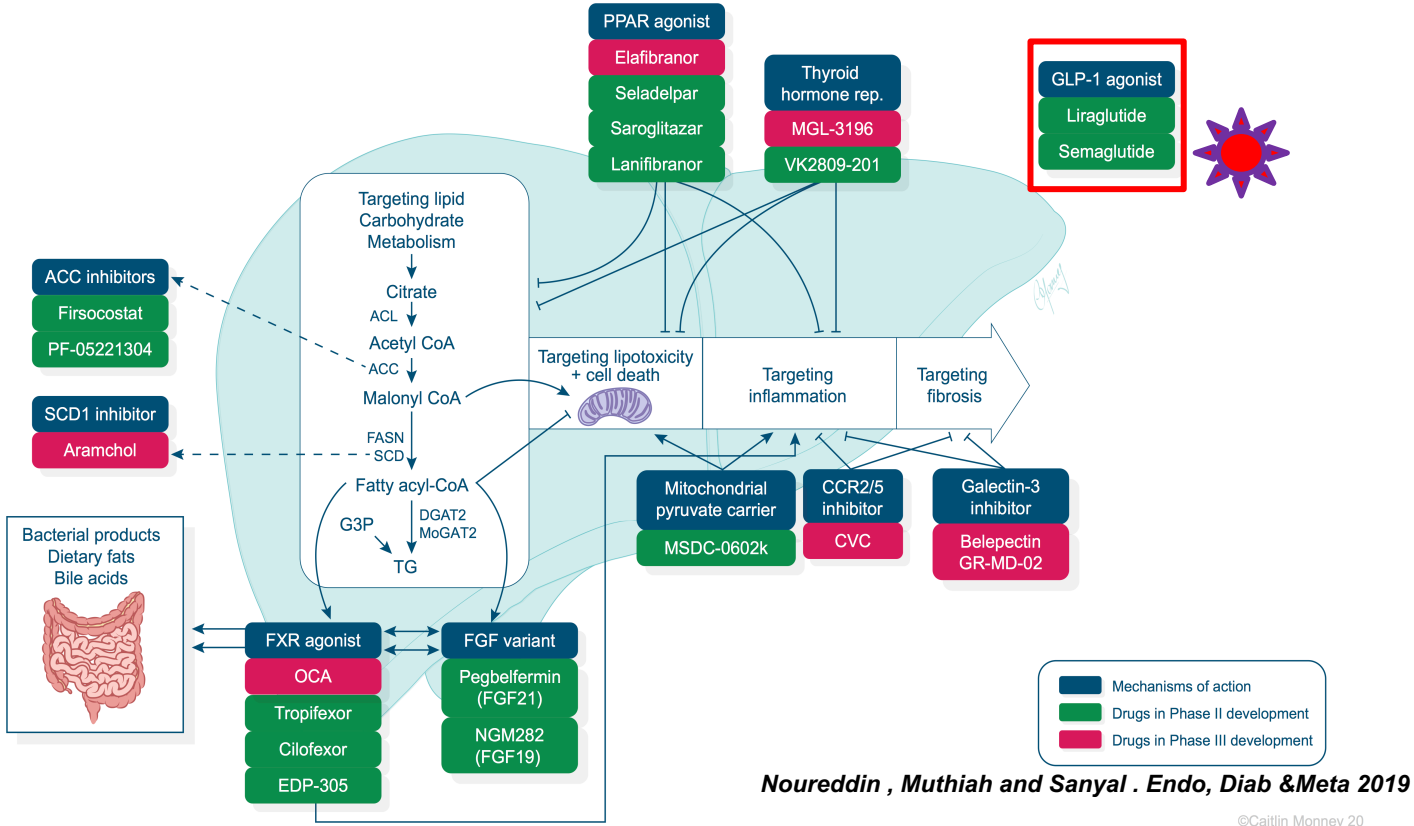
- **Statistically significant decrease of HbA1c, fasting glucose, insulin after 24 weeks**

See Poster LP9

Safety – Safety Set (N=247)

N (%) patients reporting Adverse Event (AE)	Placebo (N = 81)	800 mg (N = 83)	1200 mg (N = 83)
Any Treatment-Emergent AE (TEAE)	50 (61.7%)	59 (71.1%)	62 (74.7%)
- Drug-related TEAE	*19 (23.5%)*	*25 (30.1%)*	*23 (27.7%)*
Any TEAE leading to drug withdrawal	3 (3.7%)	4 (4.8%)	3 (3.6%)
- Drug-related TEAE leading to drug withdrawal	*2 (2.5%)*	*1 (1.2%)*	*2 (2.4%)*
Any Serious TEAE	3 (3.7%)	3 (3.6%)	7 (8.4%)
- Drug-related Serious TEAE	*2 (2.5%)*	-	-
% patients reporting the most frequent AEs (> 5% of patients in at least one lanifibranor arm)			
Diarrhoea	1 (1.2%)	8 (9.6%)	10 (12.0%)
Fatigue	8 (9.9%)	3 (3.6%)	11 (13.3%)
Nausea	3 (3.7%)	8 (9.6%)	7 (8.4%)
Weight increased [1]	-	8 (9.6%)	7 (8.4%)
Oedema peripheral [2]	2 (2.5%)	5 (6.0%)	7 (8.4%)
Headache	4 (4.9%)	4 (4.8%)	7 (8.4%)
Abdominal pain	4 (4.9%)	4 (4.8%)	5 (6.0%)
Dizziness	3 (3.7%)	2 (2.4%)	6 (7.2%)
Anaemia	-	1 (1.2%)	6 (7.2%)
Constipation	6 (7.4%)	3 (3.6%)	5 (6.0%)
Transaminases increased	1 (1.2%)	5 (6.0%)	3 (3.6%)

pharmacology); [2] 4 were considered by the investigator as related to study treatment: 2 in 800 mg and 2 in 1200 mg groups



Noureddin , Muthiah and Sanyal . Endo, Diab &Meta 2019

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Efficacy and safety of subcutaneous semaglutide once-daily versus placebo in patients with non-alcoholic steatohepatitis

Philip N. Newsome*, Kristine Buchholtz, Kenneth Cusi, Martin Linder, Takeshi Okanoue, Vlad Ratziu, Arun J. Sanyal, Anne-Sophie Sejling, Stephen A. Harrison

Abstract # 0010

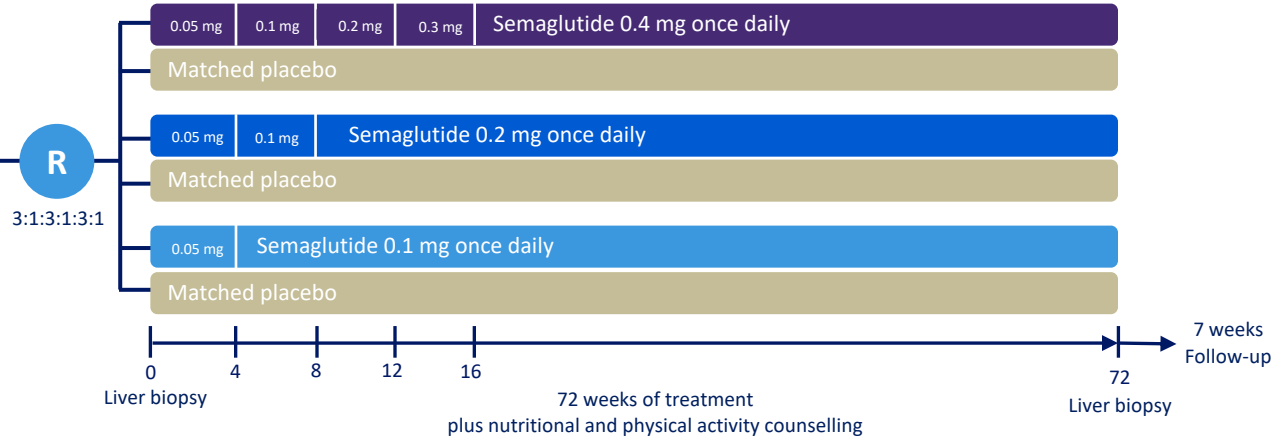
*National Institute for Health Research, Birmingham Biomedical Research Centre, Birmingham, UK

Trial design

Trial objective: To compare the effect of three different doses of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of NASH

Eligible patients

Biopsy confirmed NASH
NAS ≥ 4
Fibrosis stage 1, 2 or 3
BMI > 25 kg/m^2
HbA_{1c} ≤ 10%



Primary endpoint:

Resolution of steatohepatitis and no worsening in liver fibrosis in patients with baseline fibrosis stage 2 or 3

Confirmatory secondary endpoint:

Improvement in liver fibrosis and no worsening in steatohepatitis with baseline fibrosis stage 2 or 3

BMI, body mass index; HbA_{1c}, glycated hemoglobin; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis.

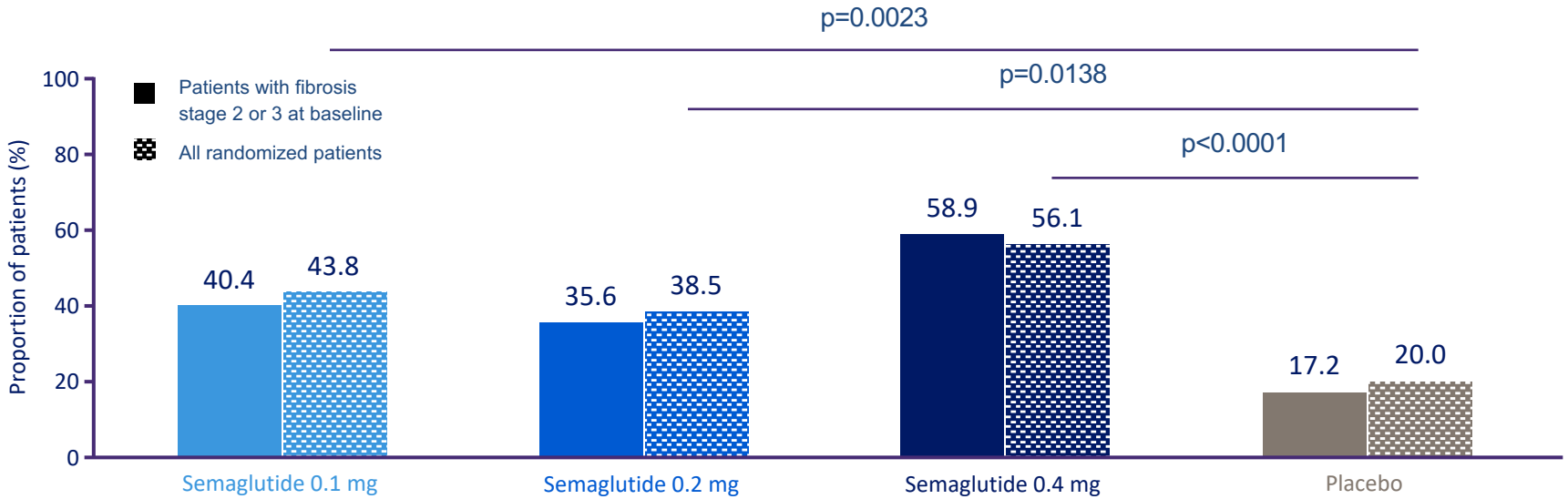
Patient disposition

	Semaglutide 0.1 mg		Semaglutide 0.2 mg		Semaglutide 0.4 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Screened									1227	
Randomised	**80**		**78**		**82**		**80**		320	
Exposed	80	(100)	78	(100)	81	(98.8)	80	(100)	319	(99.7)
Completed treatment	74	(92.5)	66	(84.6)	73	(89.0)	72	(90.0)	285	(89.1)
With evaluable biopsy at week 72	**72**	**(90.0)**	**61**	**(78.2)**	**66**	**(80.5)**	**67**	**(83.8)**	**266**	**(83.1)**
Premature treatment discontinuation	6	(7.5)	12	(15.4)	9	(11.0)	8	(10.0)	35	(10.9)
With evaluable biopsy at week 72	2	(2.5)	3	(3.8)	3	(3.7)	3	(3.8)	11	(3.4)
Primary reason – adverse event	3	(3.8)	11	(14.1)	4	(4.9)	4	(5.0)	22	(6.9)
Trial completers excluding deaths	76	(95.0)	72	(92.3)	77	(93.9)	77	(96.3)	302	(94.4)
Withdrawal from trial or death	4	(5.0)	6	(7.7)	5	(6.1)	3	(3.8)	18	(5.6)
Primary reason										
Withdrawal by subject	3	(3.8)	5	(6.4)	3	(3.7)	2	(2.5)	13	(4.1)
Lost to follow-up	1	(1.3)	0	(0.0)	2	(2.4)	1	(1.3)	4	(1.3)
Death	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)

Data based on full analysis set. N, number of patients; %, percentage of patients.

Resolution of steatohepatitis and no worsening in liver fibrosis

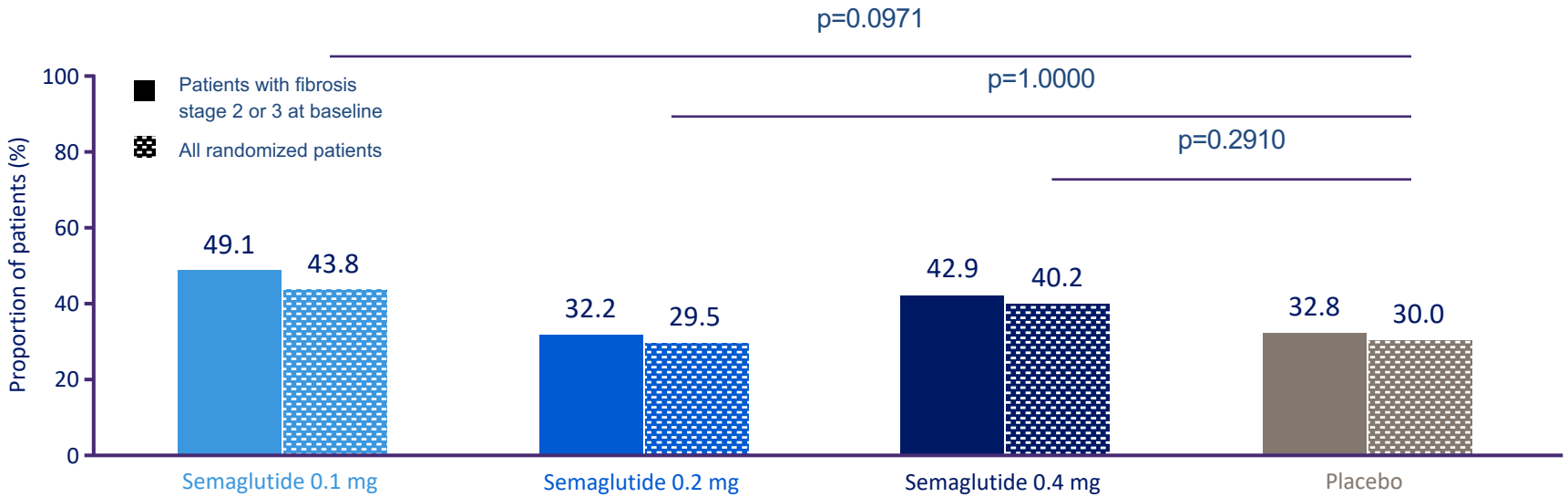
Patients with fibrosis stage 2 or 3 at baseline and all randomized patients



Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

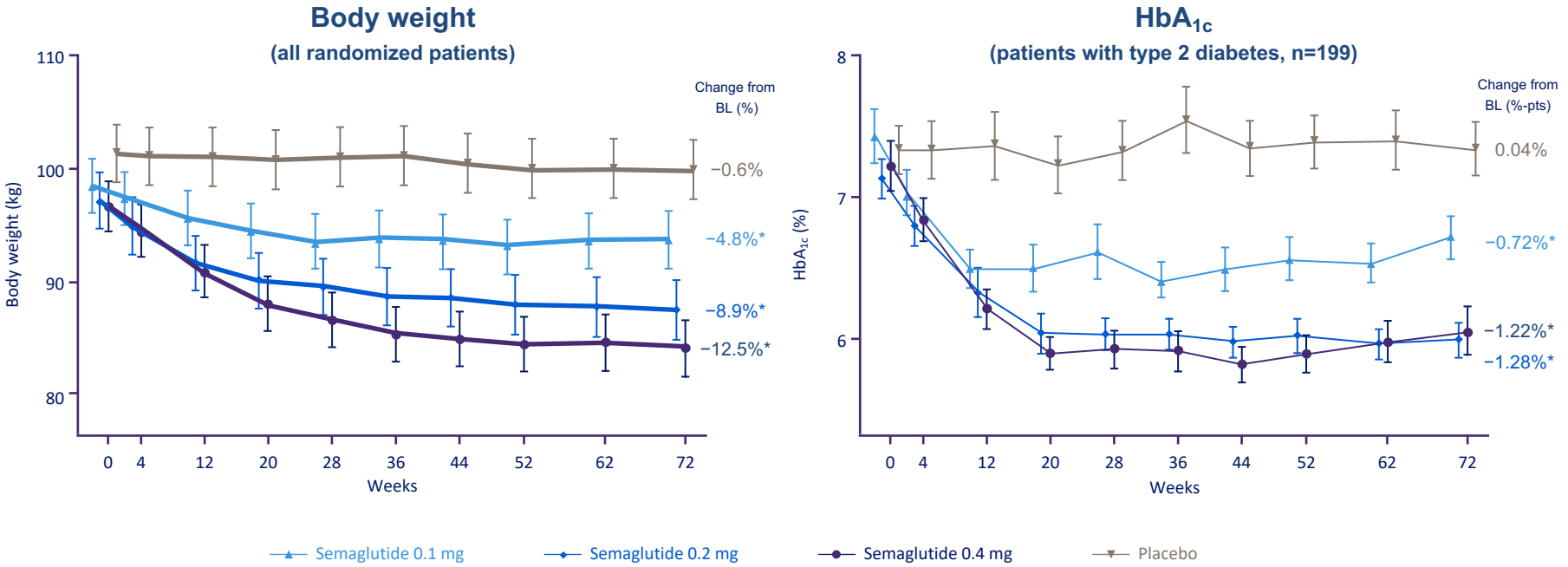
Improvement in liver fibrosis and no worsening in steatohepatitis

Patients with fibrosis stage 2 or 3 at baseline and all randomized patients



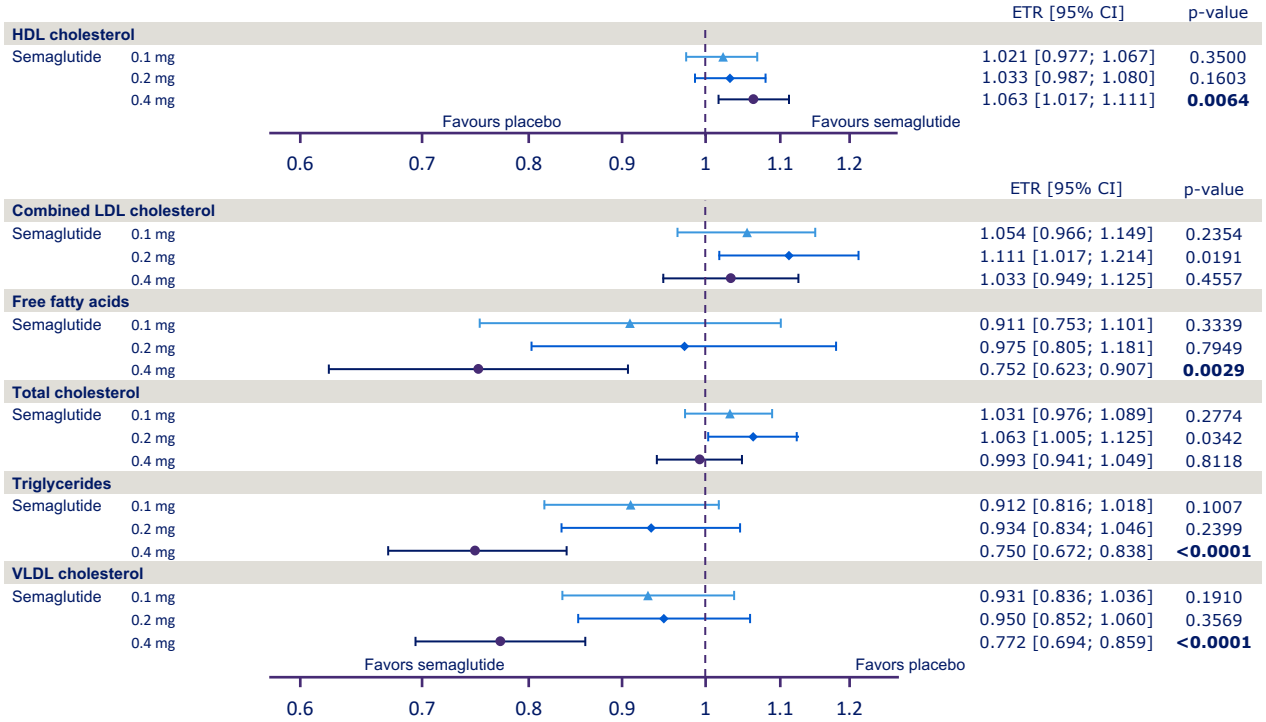
Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

Changes in body weight and HbA_{1c}



In-trial data. Data are observed means with standard error of the mean. Change from baseline values are estimated means. BL, baseline; HbA_{1c}, glycated hemoglobin.
**p<0.05 for estimated treatment difference versus placebo.*

Changes in lipids



Semaglutide 0.4 mg versus placebo

↑ HDL cholesterol

↓ free fatty acids triglycerides and VLDL cholesterol

Data based on in-trial period. Estimates taken from an ANCOVA with missing data multiply imputed from placebo group. ANCOVA, analysis of variance; CI, confidence interval; ETR, estimated treatment ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

Adverse events

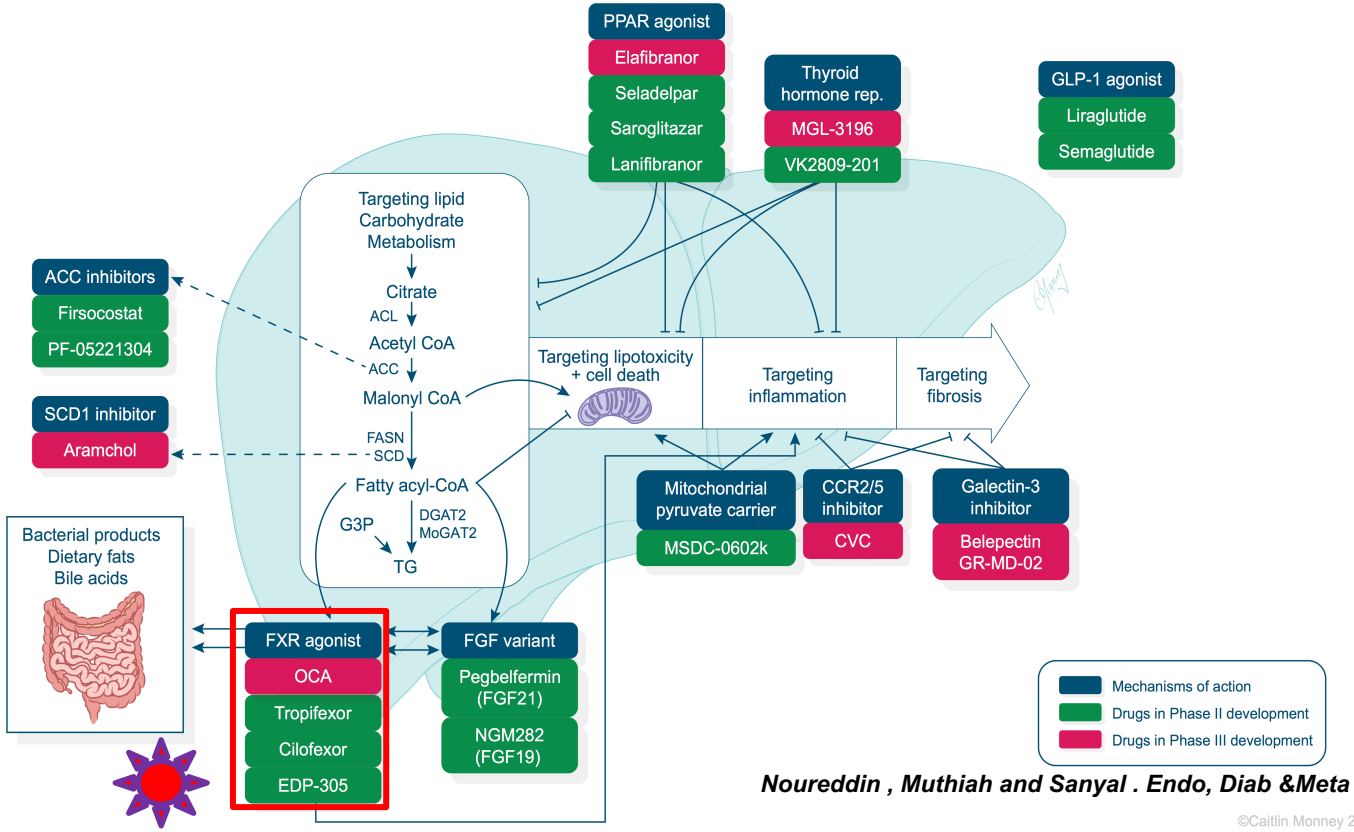
	Semaglutide 0.1 mg (N=80)				Semaglutide 0.2 mg (N=78)				Semaglutide 0.4 mg (N=81)				Placebo (N=80)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Observation time (years)	115.4				105.8				114.2				113.7			
All adverse events	72	(90.0)	525	454.9	76	(97.4)	577	545.4	76	(93.8)	511	447.6	67	(83.8)	445	391.4
Gastrointestinal disorders	51	(63.8)	152	131.7	60	(76.9)	204	192.8	55	(67.9)	191	167.3	36	(45.0)	77	67.7
Nausea	24	(30.0)			29	(37.2)			34	(42.0)			9	(11.3)		
Constipation	13	(16.3)			17	(21.8)			18	(22.2)			10	(12.5)		
Decreased appetite	16	(20.0)			18	(23.1)			18	(22.2)			4	(5.0)		
Diarrhea	23	(28.8)			22	(28.2)			16	(19.8)			11	(13.8)		
Vomiting	**14**	**(17.5)**			**17**	**(21.8)**			**12**	**(14.8)**			**2**	**(2.5)**		
Serious adverse events	**12**	**(15.0)**	**18**	**15.6**	**15**	**(19.2)**	**24**	**22.7**	**12**	**(14.8)**	**17**	**14.9**	**8**	**(10.0)**	**8**	**7.0**
Possibly/probably related to trial product	2	(2.5)	3	2.6	3	(3.8)	5	4.7	2	(2.5)	2	1.8	1	(1.3)	1	0.9
Fatal event	0				1	(1.3)	1	0.9	0				0			

All exposed patients (on-treatment) N, number of patients with at least one adverse event; %, proportion of patients with at least one adverse event; E, number of events; R, events per 100 patient years of exposure ('on-treatment').

Other safety outcomes of interest

AEs within safety focus area	Observation period	Semaglutide 0.1 mg (N=80)			Semaglutide 0.2 mg (N=78)			Semaglutide 0.4 mg (N=81)			Placebo (N=80)		
		N	(%)	R	N	(%)	R	N	(%)	R	N	(%)	R
Gallbladder related disorders	On-treatment	5	(6.3)	6.9	4	(5.1)	4.7	6	(7.4)	7.9	2	(2.5)	2.6
Acute pancreatitis[a]	On-treatment	0			0			0			0		
Hepatic events	On-treatment	9	(11.3)	12.1	6	(7.7)	9.5	7	(8.6)	8.8	11	(13.8)	15.8
Severe hypoglycemic episodes[b]													
Patients with T2D	On-treatment	2	(4.1)	2.9	1	(2.0)	2.9	0			0		
All Neoplasms		10	(12.5)	10.3	11	(14.1)	12.5	14	(17.3)	12.6	6	(7.5)	5.0
Benign neoplasms[c]													
Colorectal polyps													
Large intestine polyp	In-trial	1	(1.3)	0.9	4	(5.1)	3.6	3			0		
Colon adenoma		1	(1.3)	0.9	0			0	(3.7)	2.5	0		
Renal cyst		3	(3.8)	2.6	1	(1.3)	0.9	0			1	(1.3)	0.8
Malignant		1	(1.3)	0.9	2	(2.6)	1.8	0			0		
Allergic reactions	On-treatment	7	(8.8)	6.9	7	(9.0)	10.4	5	(6.2)	4.4	6	(7.5)	7.9
CV events[a] **(EAC-confirmed)**													
CV death	In-trial	0			1	(1.3)	0.009	0			0		
CV events		0			1	(1.3)	0.018	1	(1.2)	0.008	0		

All exposed patients (MedDRA searches and EAC-confirmed events). The results for the MedDRA search 'gastrointestinal disorders' are not shown in table. For the MedDRA searches 'abuse and misuse' and 'suspected transmission of an infectious agent' there were no events. [a]Adjudicated events; [b]According to the ADA classification; [c]Defined as 3 or more events in any treatment group. %, proportion of patients with at least one adverse event; ADA, American Diabetes Association; AE, adverse event; CV, cardiovascular; EAC, event adjudication committee; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients with at least one adverse event; R, events per 100 patient years of exposure ('on-treatment'); T2D, type 2 diabetes.



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Safety and efficacy of tropifexor in patients with fibrotic nonalcoholic steatohepatitis: 48-week results from Part C of the Phase 2 FLIGHT-FXR study

Kathryn Jean Lucas,[1] Patricia Lopez,[2] Eric Lawitz,[3] Aasim Sheikh,[4] Diego Aizenberg,[5] Stanley Hsia,[6] George Boon Bee Goh,[7] John Vierling,[8] Juan Frias,[6] Judith White,[9] Hirokazu Takahashi,[10] Donald Lazas,[11] Masato Yoneda,[12] Salvador Augustin,[13] Won Kim,[14] Juergen Loeffler,[2] Felicity Schaefer,[15] Marilyn Cines,[15] Natasha A Sahr,[15] Sophie Lamle,[2] Miljen Martic,[2] Clifford Brass,[15] and Arun J Sanyal[16]

Study population (Part C)

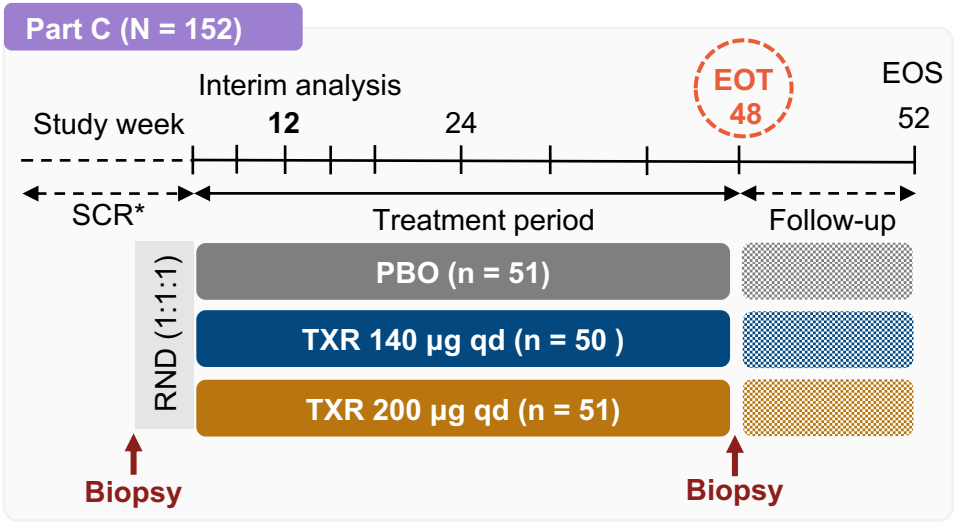
Key inclusion criteria

- Age ≥18 years
- HFF ≥10% at screening
- ALT ≥43 IU/L (males) or ≥28 IU/L (females)
- Histologic evidence of NASH* with F2/F3 fibrosis and exclusion of other chronic liver disease

Key exclusion criteria

- Uncontrolled diabetes mellitus (HbA1c ≥9.5%) within 60 days prior to enrollment
- Evidence of hepatic decompensation or severe liver impairment
- Current use or history of significant alcohol consumption
- Pregnant or nursing (lactating) women
- Previous exposure to FXR agonists (including TXR)

Study design: FLIGHT-FXR Part C



*SCR period: −10 weeks to RND

Key Primary Endpoints at W12

- ALT, AST, and HFF (MRI-PDFF)
- Safety and tolerability

Key Secondary Endpoints at W12

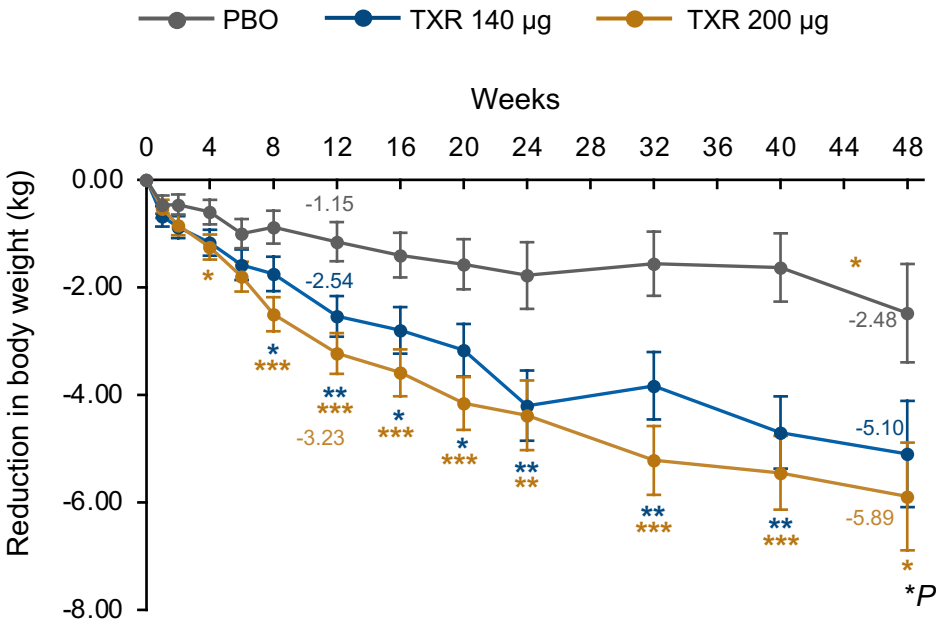
- GGT and body weight

Key Secondary Endpoints at W48

- Biomarkers: ALT and AST
- HFF (MRI-PDFF)
- **Histology*:** ≥1 point improvement in fibrosis without worsening of NASH; resolution of NASH without worsening of fibrosis
- Safety and tolerability

Body weight up to W48

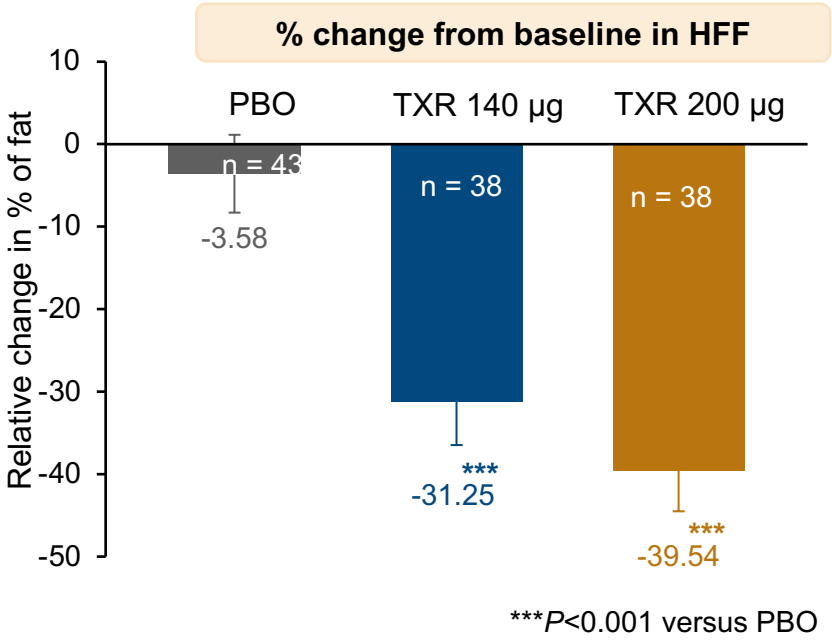
Significant, sustained decrease with tropifexor relative to placebo



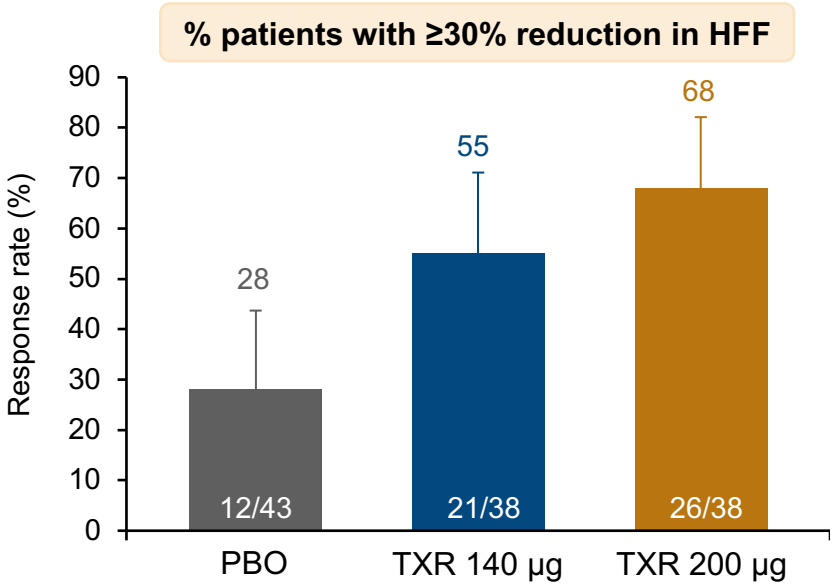
*P<0.05, **P<0.01, ***P<0.001 versus PBO

HFF (MRI-PDFF) at W48

Significant decrease with tropifexor versus placebo



***P<0.001 versus PBO

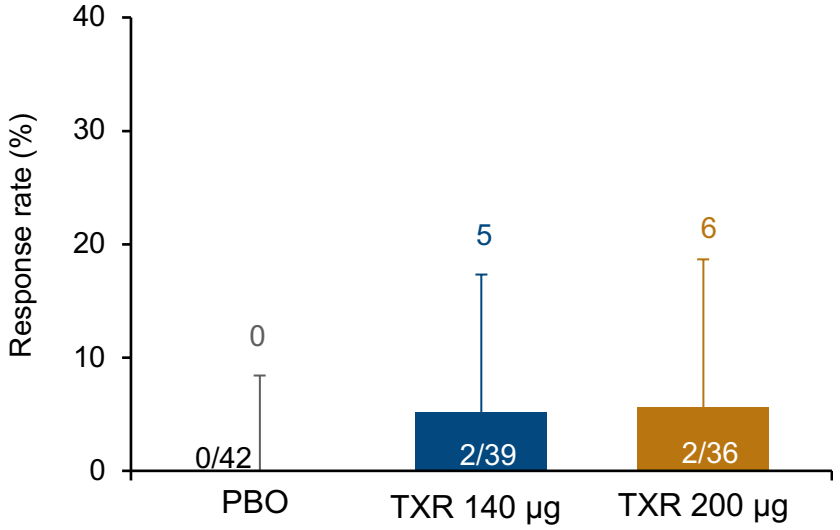


NASH resolution with no worsening of fibrosis

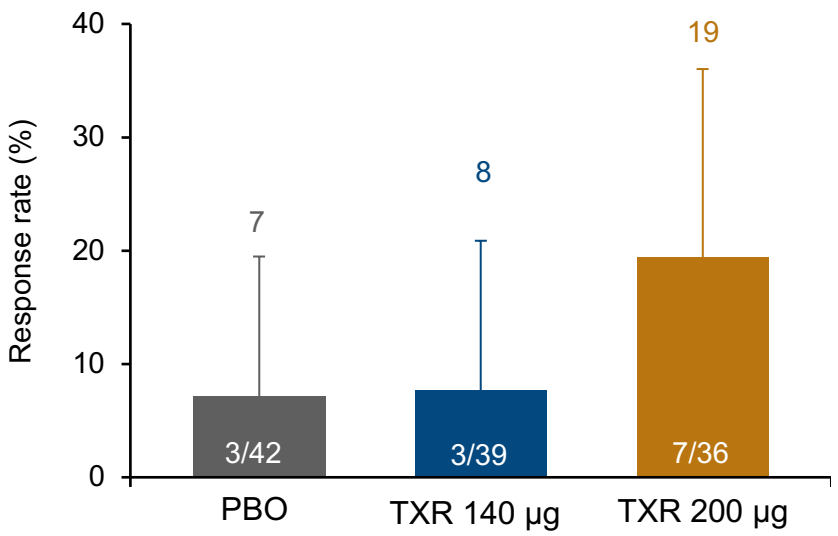
Response seen in a few patients in tropifexor groups

Central pathologist assessment

FDA and EMA definition



Pathologist diagnosis*

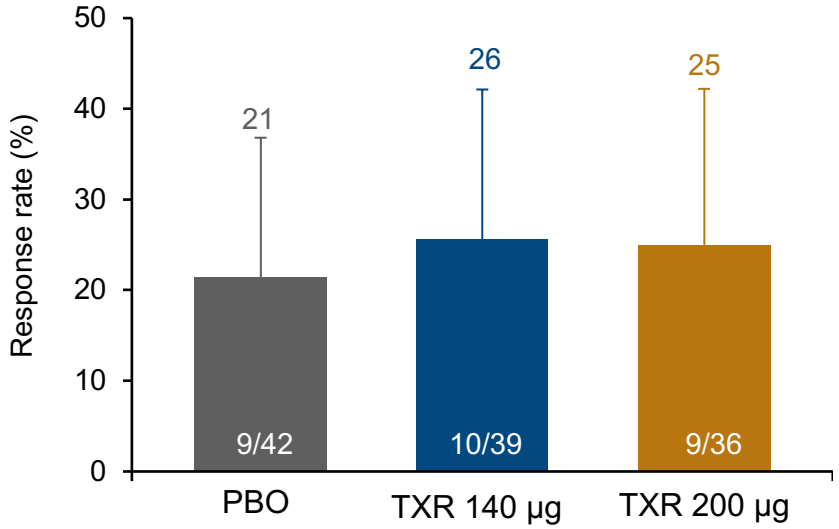


Fibrosis improvement with no worsening of NASH

No significant difference between tropifexor and placebo groups

Central pathologist assessment

≥1 point improvement in fibrosis stage (NASH CRN) with no worsening of NASH (total score)



Overall safety and tolerability up to W48

More dose reduction/treatment discontinuation in tropifexor 200 µg group

Incidence, n (%)	PBO (N = 51)	TXR 140 µg (N = 50)	TXR 200 µg (N = 51)
Number of subjects with at least one AE	46 (90)	49 (98)	49 (96)
Number of subjects with at least one SAE	6 (12)	5 (10)	3 (6)
AEs leading to dose reduction/discontinuation	**3 (6)**	**9 (18)**	**19 (37)**
AEs leading to discontinuation	**2 (4)**	**5 (10)**	**9 (18)**
Death	0	0	0
Most frequent AEs			
Pruritus	**11 (22)**	**26 (52)**	**35 (69)**
Nausea	7 (14)	6 (12)	10 (20)
Upper respiratory tract infection	8 (16)	9 (18)	3 (6)
Diarrhea	5 (10)	3 (6)	7 (14)
Nasopharyngitis	4 (8)	6 (12)	5 (10)
Fatigue	4 (8)	7 (14)	3 (6)

- Most pruritus events were of grade 1 (mild) severity. **Treatment discontinuation rates due to pruritus were low (PBO, 0%; TXR 140 µg 6% [n = 3]; TXR 200 µg, 8% [n = 4])**
- **Decrease of HDL-C and increase of LDL-C with TXR were stabilized after W12**
- Very few patients were initiated on lipid-lowering drugs* during the study (PBO, n = 1; TXR 140 µg, n = 0; TXR 200 µg, n = 2)

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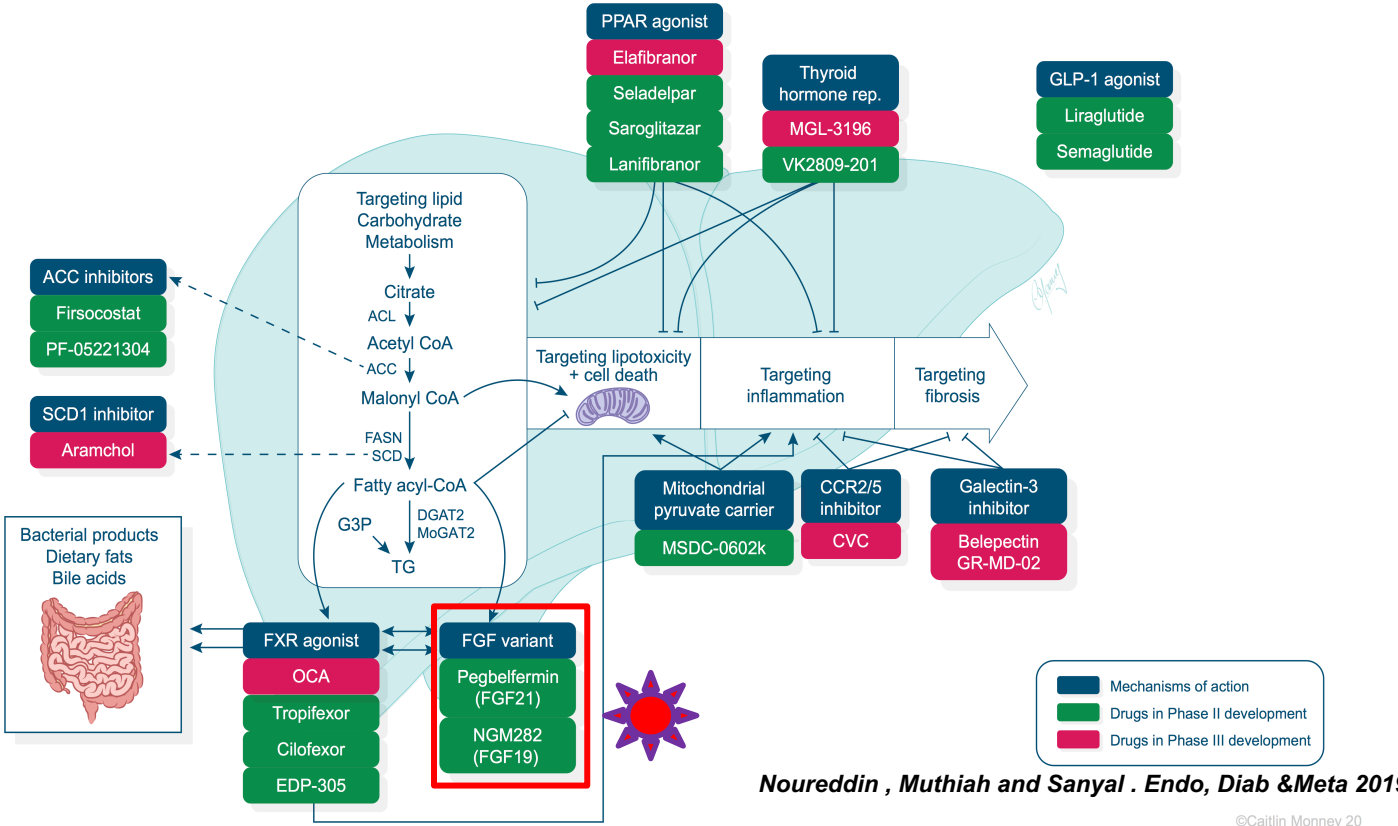

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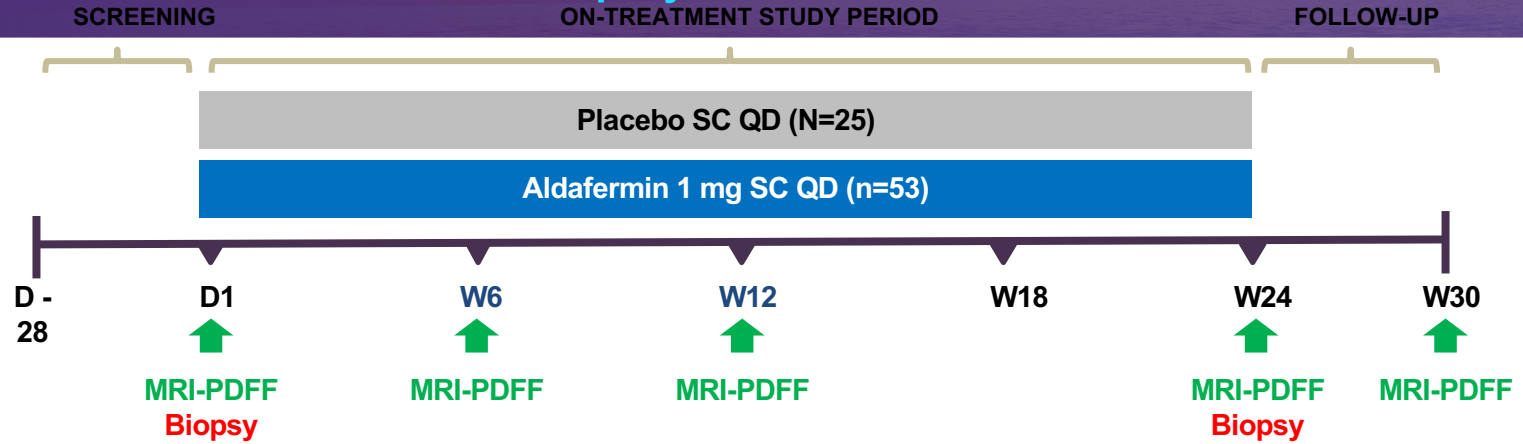
Final analysis of a 24-week, randomized, double-blind, placebo-controlled, multicenter study of aldafermin (NGM282) in patients with nonalcoholic steatohepatitis
Abstract 0072

Stephen A. Harrison[1,2], Guy Neff[3], Cynthia D. Guy[4], Mustafa Bashir[5], Nadege Gunn[2], Angelo H. Paredes[6], Ziad Younes[7], Juan P. Frias[8], James F. Trotter[9], Anita Kohli[10], Sam E. Moussa[11], Kristin Nelson[12], Mildred Gottwald[12], William Chang[12], Andrew Z. Yan[12], Alex M. DePaoli[12], Lei Ling[12] and Hsiao D. Lieu[12]

Cohort 4: A 24-Week Phase 2 Study of Aldafermin in Patients with Biopsy-Proven NASH



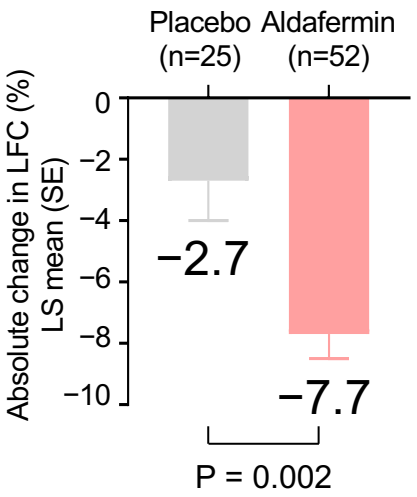
Safety population	N=78	Aldafermin : placebo (2:1)
Efficacy population	N=77	At least one dose and valid post-dose efficacy value
Liver histology population	N=72	Valid, non-missing biopsy at baseline and W24

- Key inclusion criteria include:
  - Biopsy-confirmed NASH with NAS ≥ 4 (1 point in each component); stage 2 or 3 liver fibrosis (F2 or F3 by NASH CRN criteria)
  - Absolute liver fat content (LFC) ≥ 8% by MRI-PDFF
  - ALT ≥ 19 IU/L in females, ALT ≥ 30 IU/L in males
- **Primary endpoint**: change from baseline in absolute LFC (as measured by MRI-PDFF) at W24
- **Secondary and exploratory endpoints** include liver histology, ALT, AST and biomarkers of fibrosis at W24
- **Rosuvastatin (ROS 20 mg) started at W2 if low-density lipoprotein cholesterol (LDL-C) rise of 10 mg/dL observed**

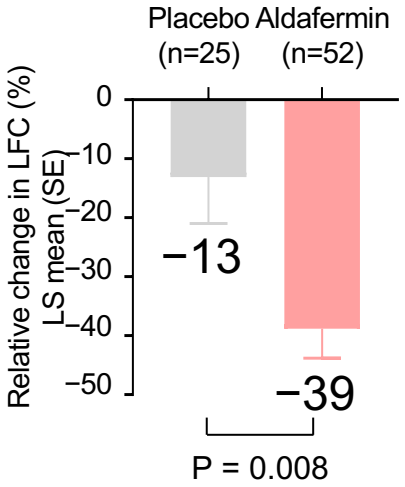
Cohort 4 Primary Endpoint Met: Achieved Statistically Significant Reduction in Absolute Liver Fat Content Reduction at Week 24

Liver Fat Content (LFC) by MRI-PDFF

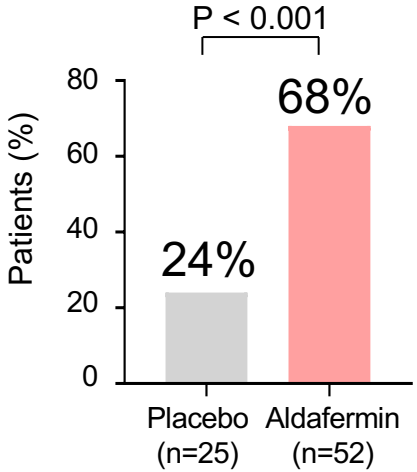
Absolute LFC



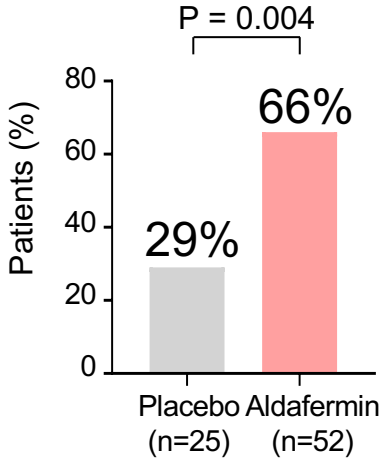
Relative LFC



↓ Absolute LFC ≥ 5%



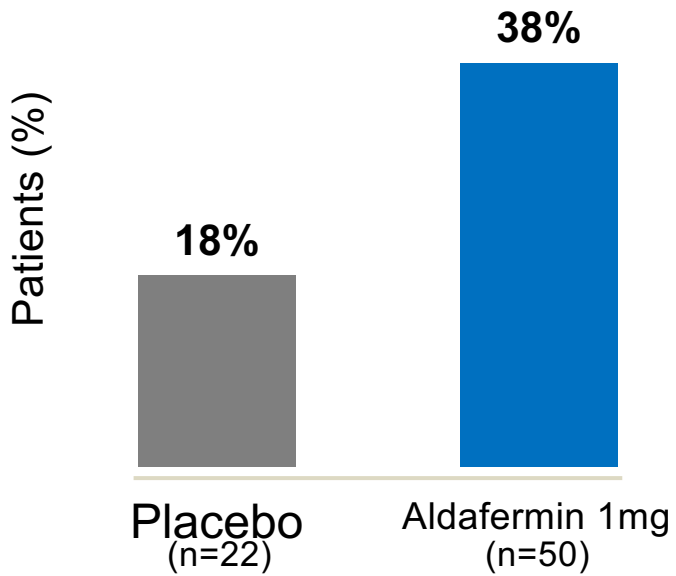
↓ Relative LFC ≥ 30%



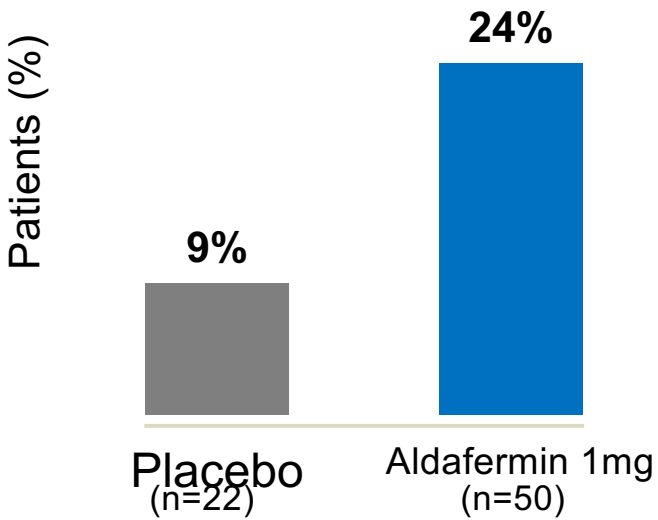
[1] Liver fat content (LFC) as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)

Cohort 4: Rapid and Consistent Improvement in Fibrosis or NASH Resolution at Week 24

Fibrosis Improvement ≥ 1 Stage with No Worsening of NASH[1]



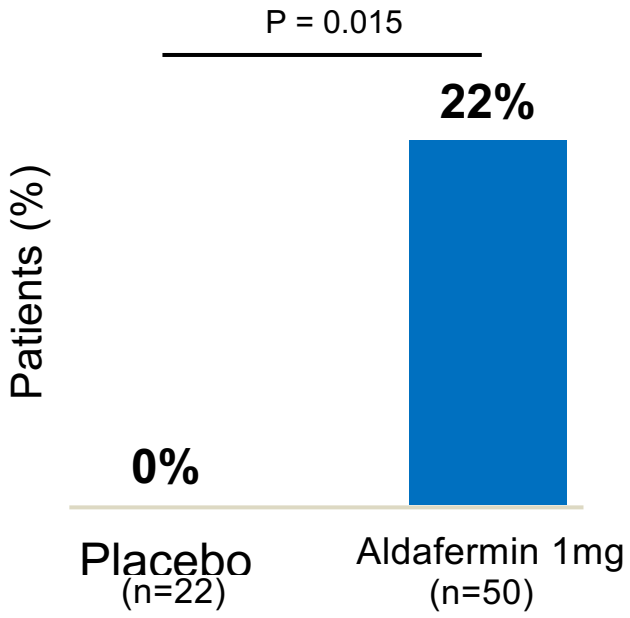
Resolution of NASH with No Worsening of Fibrosis[1]



Liver Histology Population (n=50 aldafermin *vs.* n=22 placebo)
[1]Defined by NASH CRN criteria; all biopsies were read blinded to treatment assignment and patient information (not powered for statistical significance)

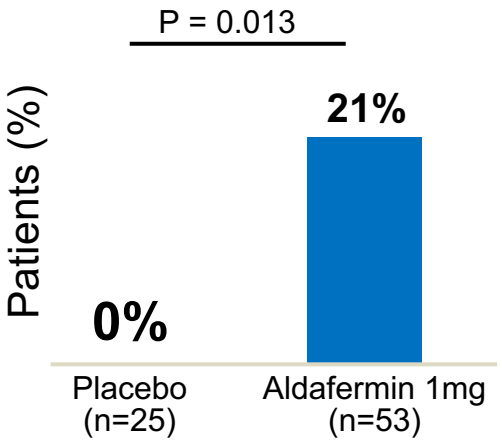
Cohort 4: Achieved Statistically Significance in Both Fibrosis Improvement AND Resolution of NASH

Both Fibrosis Improvement ≥ 1 stage AND Resolution of NASH[1] at Week 24

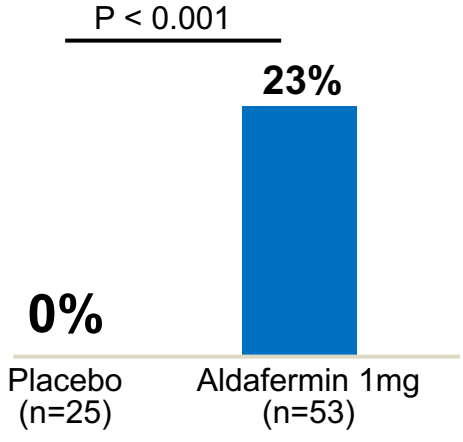


Sensitivity analysis

Patients who did not have end-of-treatment biopsies were imputed as non-responders (intention-to-treat principle)



Multiple imputation with missing-at-random assumption



[1] Defined as patients who have an improvement in liver fibrosis by ≥1 stage AND have a NAS score of 0 or 1 for inflammation and 0 for ballooning at W24 (not powered for statistical significance);

Cohort 4: Aldafermin Well Tolerated and Adverse Events Generally Comparable to Placebo

TEAE Classification	Placebo (N=25)	Aldafermin 1 mg (N=53)
Any TEAE	22 (88.0%)	46 (86.8%)
TEAE Leading to Drug Withdrawal	1 (4.0%)	0
Serious Adverse Event (SAE)[1]	3 (12.0%)	2 (3.8%)
Drug-Related TEAE	11 (44.0%)	27 (50.9%)
TEAE Leading to Death	0	0

Most Common (>10%) Adverse Events	Placebo (N=25)	Aldafermin 1 mg (N=53)
Diarrhea	6 (24.0%)	15 (28.3%)
Nausea	6 (24.0%)	5 (9.4.%)
Headache	9 (36.0%)	7 (13.2%)
Fatigue	4 (16%)	3 (5.7%)
Abdominal Distension	3 (12.0%)	7 (13.2%)
Diabetes Mellitus	5 (20.0%)	2 (3.8%)
Peripheral Edema	3 (12.0%)	2 (3.8%)

[1] SAEs: Placebo (mental status changes; appendicitis; anxiety); Aldafermin (rectal bleeding; liver biopsy procedure-related complication)

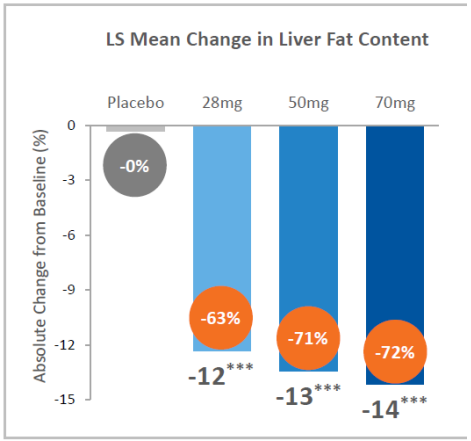
- All SAEs were deemed to be not related to treatment by site investigator

Aldafermin Safety

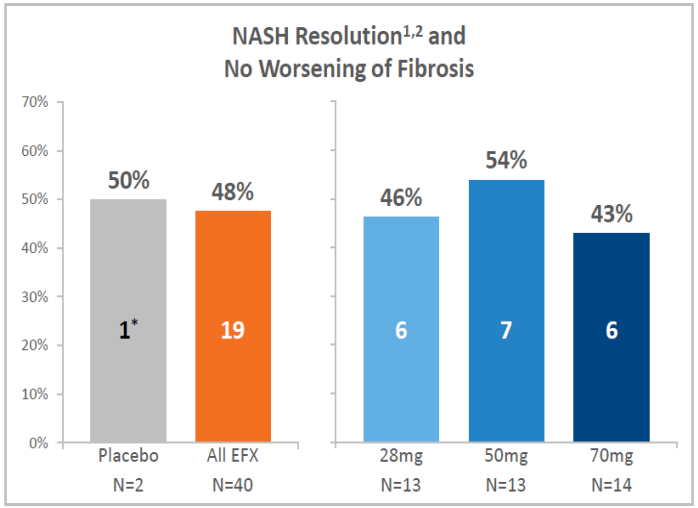
- No increase in gastrointestinal adverse events
- No increase in pruritus (4% aldafermin *vs.* 8% placebo)
- Mechanism-based increase in LDL-C due to blocking of conversion from cholesterol to bile acids required rosuvastatin in most patients (**Poster #1678**)

Efruxifermin (EFX), a long-acting Fc-FGF21 fusion protein, administered for 16 weeks to patients with NASH substantially reduces liver fat and ALT, and improves liver histology: analysis of a randomized, placebo-controlled, Phase 2a study (BALANCED). Harrison S, et al. Abstract # 0008

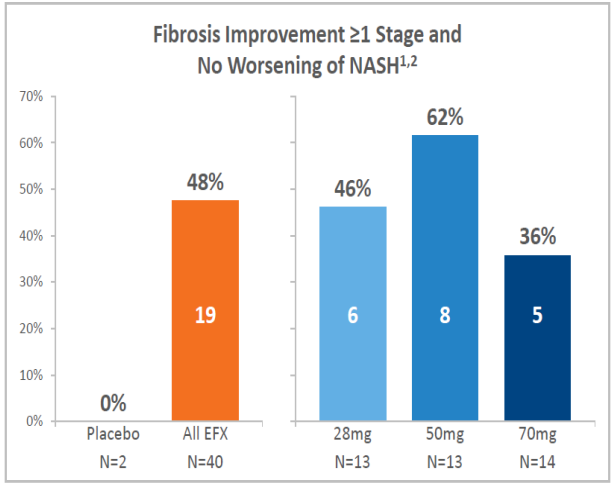
- EFX is an engineered FGF21 with Q week dosing.
- Treatment duration up to 16 weeks. MRI @ week 12 and a biopsy @ W16 if ≥ relative reduction in HFF
- Placebo=20; EFX 28mg = 20 ; EFX50mg = 20; EFX70 mg = 20 [EOT Bx = 2, 13, 13, 14]



*** p<0.001 versus placebo (ANCOVA)



[1] NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning
[2] Secondary and exploratory histological endpoints were not powered for statistical significance
* A single placebo responder lost 25 pounds over 16 weeks (11% weight reduction)

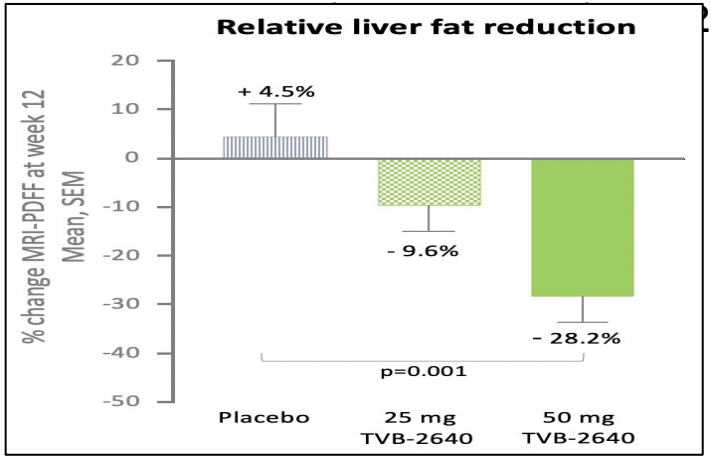


[1] Improvement in liver fibrosis greater than or equal to one stage and no worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis)
[2] Secondary and exploratory histological endpoints were not powered for statistical significance

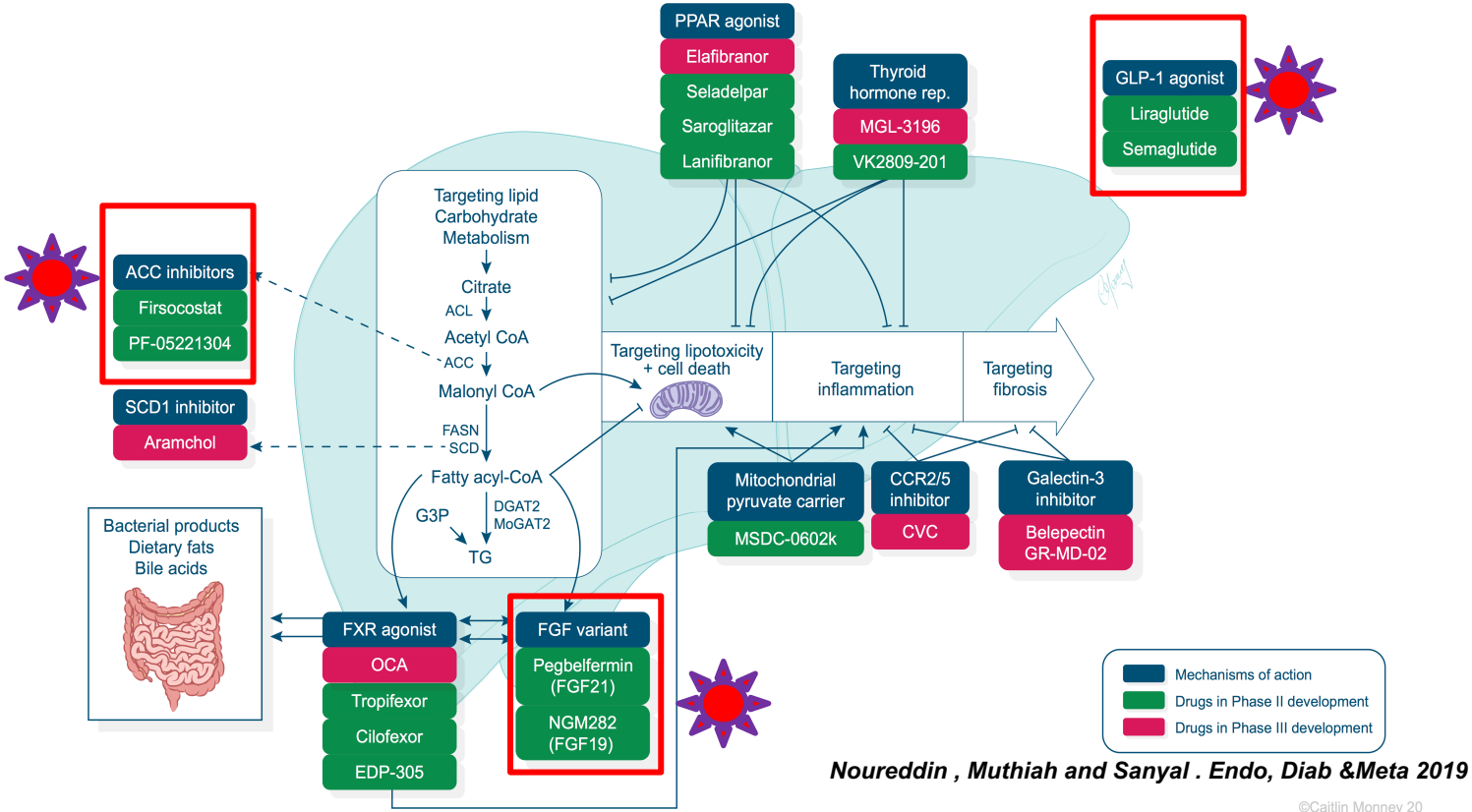
- ~ 10% discontinuation in EFX group due to TEAEs. No safety signals reported.

Novel, first-in-class, fatty acid synthase (FASN) inhibitor, TVB-2640 demonstrates clinically significant reduction in liver fat by MRI-PDFF and ALT in NASH: A phase 2 randomized, placebo-controlled trial (FASCINATE-1).

- Increased hepatic de novo lipogenesis (DNL) increases liver fat and has been linked to lipotoxicity, a hallmark of nonalcoholic steatohepatitis (NASH). TVB-2640 is an oral, once-daily, first-in-class small molecule fatty acid synthase (FASN) inhibitor that decreases DNL in humans.
- 91 patients randomized to placebo, or TVB-25 mg QD or 50 mg QD for 12 weeks. Primary end points were safety and changes in HFF by MRI PDFF.
- Relative reduction in HFF: Placebo: 4.5%, TVB25: 9.6% and TVB50: 28.2% (p=0.001)
- 25: 23% and TVB50: 61% (p=0.001)
  - Favorable changes in ALT, lipids, adiponectin, fibrosis and inflammation markers
  - Serum tripalmitin, a marker of DNL, was reduced with TVB
  - Well tolerated and no safety signals noted



Loomba R, et al. Abs # 0067



Noureddin , Muthiah and Sanyal . Endo, Diab &Meta 2019

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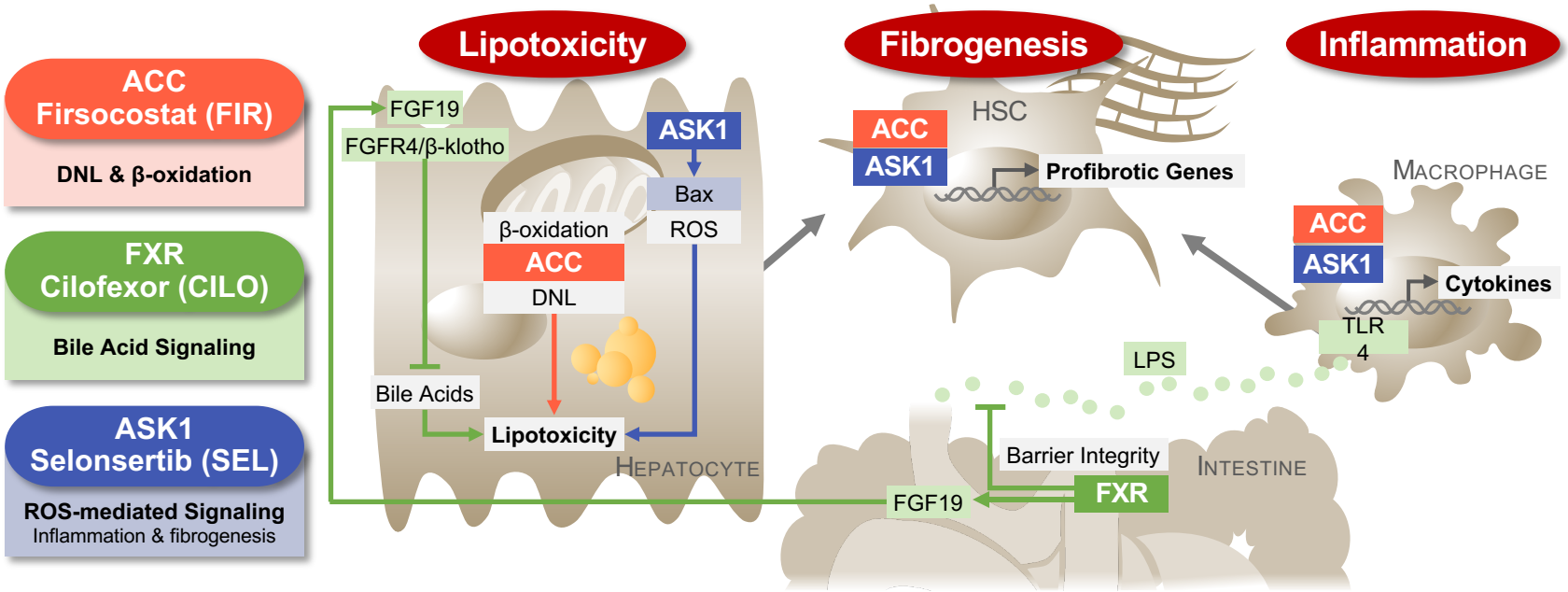
Safety and Efficacy of Combination Therapies Including Cilofexor/Firsocostat in Patients With Bridging Fibrosis and Cirrhosis Due to NASH: Results of the Phase 2b ATLAS Trial

Rohit Loomba,[1] Mazen Noureddin,[2] Kris V. Kowdley,[3] Anita Kohli,[4] Aasim Sheikh,[5] Guy Neff,[6] Bal Raj Bhandari,[7] Nadege Gunn,[8] Stephen H. Caldwell,[9] Zachary Goodman,[10] IlanWapinski,[11] Murray Resnick,[11] Andrew H. Beck,[11] Dora Ding,[12] Catherine Jia,[12] Ryan S. Huss,[12] Chuhan Chung,[12] G. Mani Subramanian,[12] Robert P. Myers,[12] Keyur Patel,[13] Brian B. Borg,[14] ReemGhalib,[15] Heidi Kabler,[16] John Poulos,[17] Ziad Younes,[18] Magdy Elkhashab,[19] TarekHassanein,[20] Rajalakshmi Iyer,[21] Peter J Ruane,[22] Mitchell L. Shiffman,[23] Simone Strasser,[24] Vincent Wai-Sun Wong,[25] Naim Alkhouri,[26] for the ATLAS Investigators

Background: Rationale for Combination Therapy in NASH

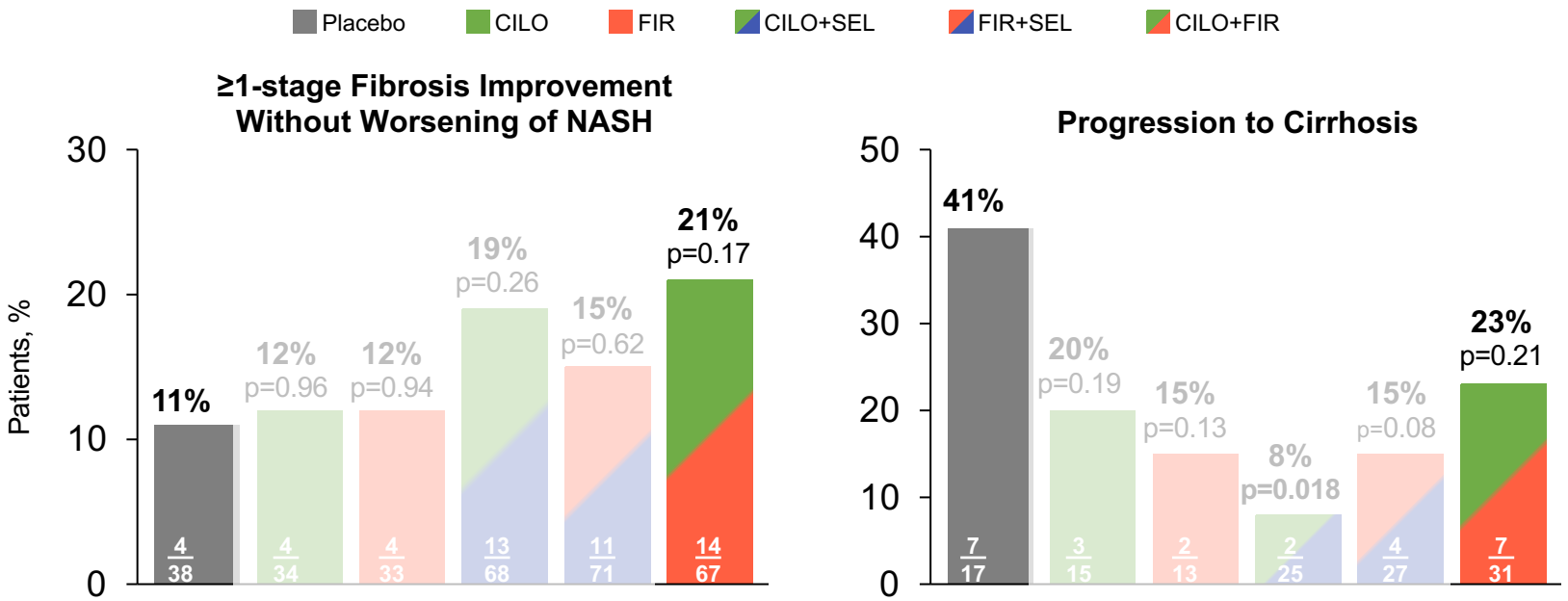


- Pathogenesis of NASH is multifactorial and patient population is heterogeneous[1]
- Firsocostat, cilofexor, and selonsertib target distinct mechanisms

ACC, acetyl-CoA carboxylase; ASK1, apoptosis signal-regulating kinase 1; DNL, de novo lipogenesis; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; HSC, hepatic stellate cell; ROS, reactive oxygen species; TLR, toll-like receptor.

1. Marra F. J Hepatol 2018;68:280-95.

Fibrosis Regression and Progression to Cirrhosis



- CILO+FIR led to highest rate of fibrosis regression, but not statistically significant vs placebo
- Reduced progression to cirrhosis vs placebo in all groups, significant for CILO+SEL

All p-values vs placebo adjusted for baseline (BL) diabetes and cirrhosis status.

Safety and Efficacy of Combination Therapies Including Semaglutide, Cilofexor, and Firsocostat in Patients with NASH

Naim Alkhouri,[1] Robert Herring,[2] Heidi Kabler,[3] Zeid Kayali,[4] Tarek Hassanein,[5] Anita Kohli,[1]Ryan Huss,[6] Yanni Zhu,[6] Jun Xu, [6] Lars Holm Damgaard,[7] Kristine Buchholtz,[7] Mette Skalshøi Kjær,[7] Clare Balendran,[7] Robert P. Myers,[6] Rohit Loomba,[8] Mazen Noureddin[9]

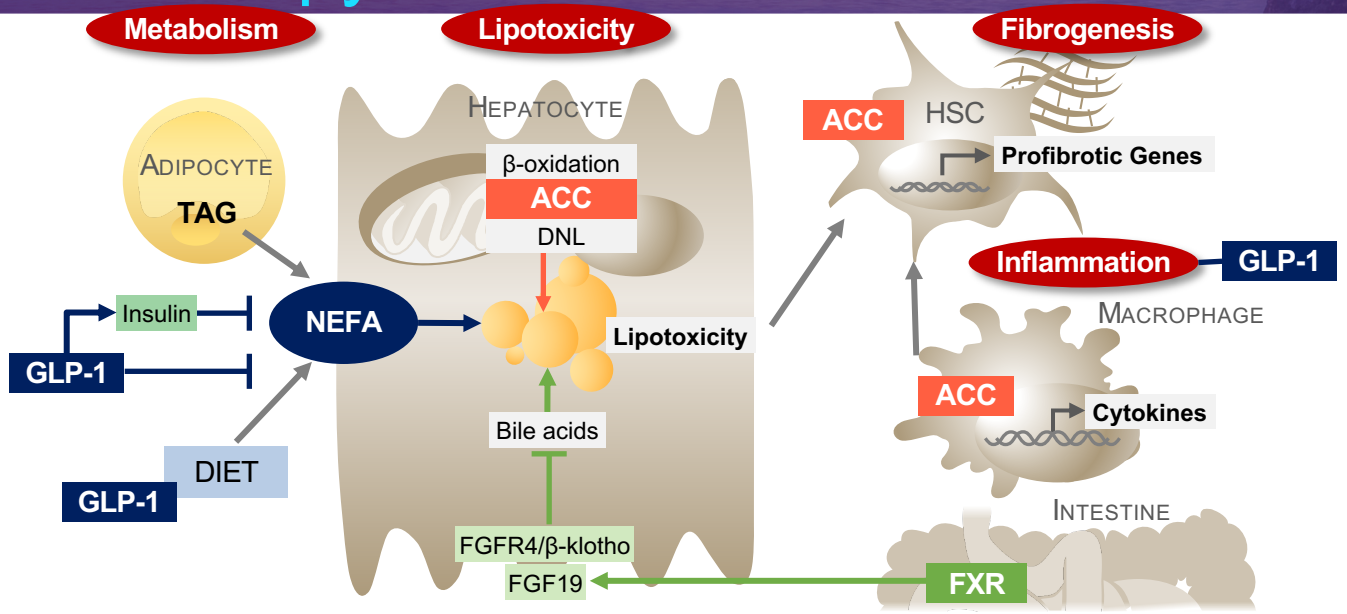
The Liver Meeting, 13–16 November 2020: Abstr LO2

Background: Rationale for Combination Therapy in NASH

GLP-1 — **Semaglutide (SEMA)**
Metabolic (weight loss, insulin sensitivity, glucose), anti-inflammatory effects, CV risk reduction*[1,2]

ACC — **Firsocostat (FIR)**
DNL & β-oxidation

FXR — **Cilofexor (CILO)**
Bile acid signaling



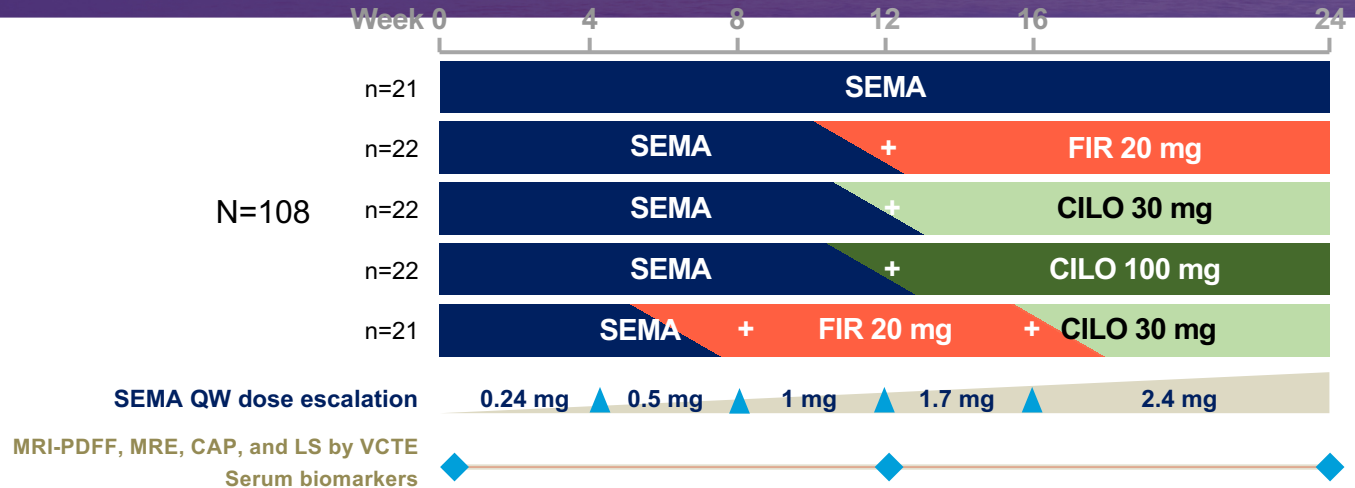
- Pathogenesis of NASH is multifactorial and patient population is heterogeneous[3]
- Semaglutide, firsocostat, and cilofexor target distinct and complementary mechanisms[4–6]

*CV risk reduction in patients with type 2 diabetes and high CV risk[1]

ACC, acetyl-CoA carboxylase; CV, cardiovascular; DNL, de novo lipogenesis; FGF19, fibroblast growth factor 19; FGFR4, FGF receptor 4; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HSC, hepatic stellate cell; NASH, non-alcoholic steatohepatitis; NEFA, non-esterified fatty acids; TAG, triacylglycerol.

1. Marso SP, et al. N Engl J Med 2016;375:1834–44; 2. Rakipovski G, et al. JACC Basic Transl Sci 2018;3:844–57; 3. Marra F. J Hepatol 2018;68:280–95; 4. Newsome PN, et al. AASLD 2020, abstr 10; 5. Loomba R, et al. Gastroenterology 2018;155:1463–73; 6. Patel K, et al. Hepatology 2020;72:58–71.

Study Design



- Key inclusion criteria
  - Histologically confirmed NASH with NASH CRN F2–F3 fibrosis (or equivalent), **or**
  - Clinical diagnosis of NAFLD, MRI-PDFF ≥10%, LS by VCTE ≥7.0 kPa, and FibroTest <0.75
- Randomization stratified by diabetes mellitus (1:1:1:1:1); open label

CAP, Controlled Attenuation Parameter; CILO, cilofexor; CRN, Clinical Research Network; FIR, firsocostat; LS, liver stiffness; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; QW, once weekly; SEMA, semaglutide; VCTE, vibration-controlled transient elastography.

Endpoints and Assessments

Primary Endpoint	Safety and tolerability
Exploratory Endpoints	
Imaging	▪ MRI-PDFF ▪ 2D MRE ▪ LS and CAP by VCTE (FibroScan) ▪ FAST score[1]
NITs and other biomarkers	▪ Liver biochemistry ▪ ELF ▪ CK18 M30 ▪ Lipids and glycemic parameters

CAP, Controlled Attenuation Parameter; CK, cytokeratin; ELF, Enhanced Liver Fibrosis score; FAST, FibroScan-aspartate aminotransferase; LS, liver stiffness; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NIT, noninvasive test of fibrosis; VCTE, vibration-controlled transient elastography.

1. Newsome PN, et al. Lancet Gastroenterol Hepatol 2020;5:362–73.

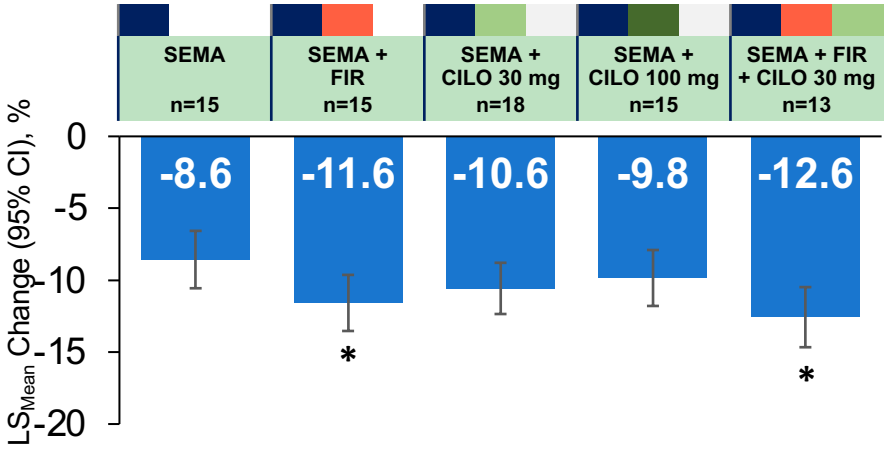
Baseline Demographics and Clinical Characteristics

		SEMA n=21	SEMA + FIR n=22	SEMA + CILO 30 mg n=22	SEMA + CILO 100 mg n=22	SEMA + FIR + CILO 30 mg n=21
Demographics	Age, y	57 (51, 61)	53 (47, 60)	53 (46, 58)	58 (46, 61)	53 (49, 61)
	Female, n (%)	15 (71)	15 (68)	16 (73)	13 (59)	15 (71)
	Hispanic, n (%)	8 (38)	12 (55)	5 (23)	7 (32)	11 (52)
	Diabetes, n (%)	11 (52)	13 (59)	12 (55)	12 (55)	11 (52)
	Body weight, kg	91.4 (77.2, 104.8)	91.3 (79.7, 112.7)	87.9 (80.7, 115.3)	98.4 (83.1, 114.3)	113 (92.9. 116.2)
Liver Parameters	ALT, U/L	60 (48, 98)	45 (29, 76)	53 (40, 86)	40 (24, 74)	42 (35, 70)
	AST, U/L	50 (36, 61)	43 (26, 51)	41, (31, 57)	27 (22, 53)	34 (27, 44)
	MRI-PDFF, %	15.3 (9.9, 19.5)	18.1 (12.5, 24.3)	19.3 (13.5, 27.1)	18.0 (14.5, 23.9)	15.9 (12.3, 25.4)
	MRE, kPa	2.75 (2.36, 3.29)	3.01 (2.59, 3.75)	2.97 (2.27, 3.80)	2.53 (2.38, 2.97)	2.91 (2.57, 3.57)
	LS by VCTE, kPa	7.7 (7.2, 10.0)	9.4 (8.1, 11.3)	8.8 (7.6, 14.1)	10.5 (7.6, 12.5)	10.7 (8.8, 12.3)
	ELF	9.6 (9.0, 10.1)	9.4 (8.6, 9.9)	9.4 (8.8, 10.1)	9.4 (8.9, 9.7)	9.4 (8.9, 9.9)
Metabolism	HbA_{1c}, %	6.1 (5.8, 6.7)	6.3 (5.9, 7.3)	6.3 (5.7, 7.7)	6.5 (5.6, 7.8)	6.3 (5.9, 7.5)
	LDL, mg/dL	101 (85, 129)	103 (71, 113)	91 (72, 112)	87 (71, 111)	107 (81, 134)
	Triglycerides, mg/dL	167 (104, 230)	160 (116, 212)	179 (114, 260)	177 (137, 225)	155 (131, 197)

Continuous data are median (Q1, Q3). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CILO, cilofexor; ELF, Enhanced Liver Fibrosis score; FIR, firsocostat; HbA_{1c}, glycated hemoglobin; LDL, low-density lipoprotein; LS, liver stiffness; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; SEMA, semaglutide; y, years.

MRI-PDFF: Greater Improvements with Combinations

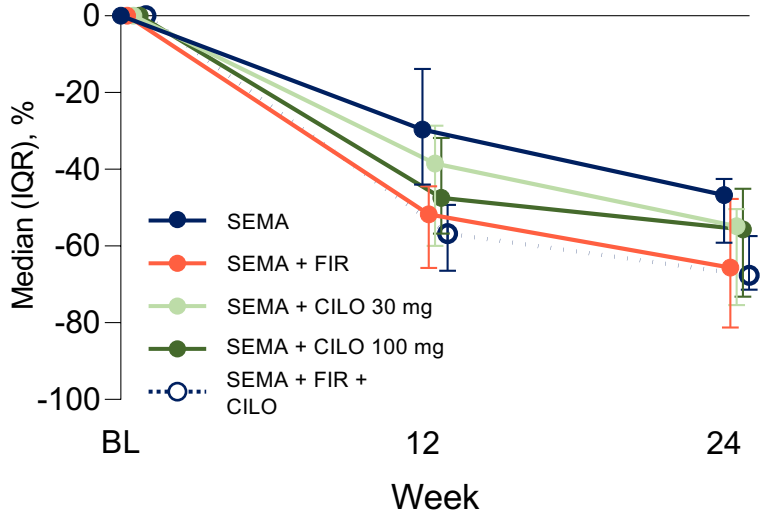
Absolute Change at Week 24



PDFF Responder Rates at Week 24, n (%)

≥30% ↓	12 (80)	14 (93)	17 (94)	13 (87)	12 (92)
≥50% ↓	6 (40)	10 (67)	14 (78)	8 (53)	11 (85)
≥70% ↓	1 (7)	4 (27)	6 (33)	5 (33)	4 (31)

Relative Change from Baseline



- Greatest reductions in PDFF in FIR groups
  - Similar findings observed with CAP

Data collected beyond 30 days after last dose of any study drug excluded from analysis. Changes in PDFF based on ANCOVA models adjusted for BL and diabetes status.
* p<0.05 vs SEMA alone. ANCOVA, analysis of covariance; BL, baseline; CAP, Controlled Attenuation Parameter; CI, confidence interval; CILO, cilofexor; FIR, firsocostat; IQR, interquartile range; LSmean, least squares mean; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; SEMA, semaglutide.

Greater Improvements in ALT, AST, and CK-18 with Combinations

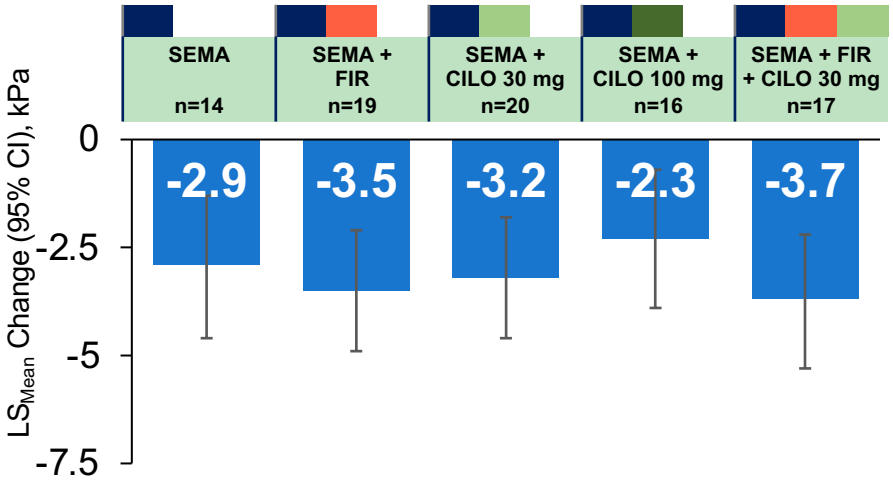
LS_{Mean} (95% CI) change from BL at week 24	SEMA n=21	SEMA + FIR n=22	SEMA + CILO 30 mg n=22	SEMA + CILO 100 mg n=22	SEMA + FIR + CILO 30 mg n=21
ALT, U/L	–13 (–23, –3)	–37* (–45, –28)	–32* (–40, –24)	–32* (–40, –23)	–40* (–49, –32)
AST, U/L	–11 (–20, –2)	–26* (–34, –18)	–21 (–29, –14)	–19 (–27, –11)	–26* (–35, –18)
GGT, U/L	–22 (–38, –6)	–21 (–36, –6)	–40 (–54, –26)	–25 (–41, –9)	–23 (–38, –8)
ALP, U/L	–7 (–20, 6)	3 (–8, 15)	–2 (–13, 9)	20* (8, 32)	17* (5, 29)
CK18 M30, U/L	–179 (–252, –107)	–312* (–381, –243)	–259 (–323, –194)	–213 (–284, –143)	–247 (–318, –176)
ELF	–0.56 (–0.86, –0.27)	–0.59 (–0.87, –0.30)	–0.46 (–0.73, –0.19)	–0.47 (–0.76, –0.19)	–0.42 (–0.70, –0.13)

- Significantly greater reductions in ALT in all combination groups vs SEMA alone
- Significant reductions from BL in ELF in all groups ($p<0.05$); however, no differences vs SEMA

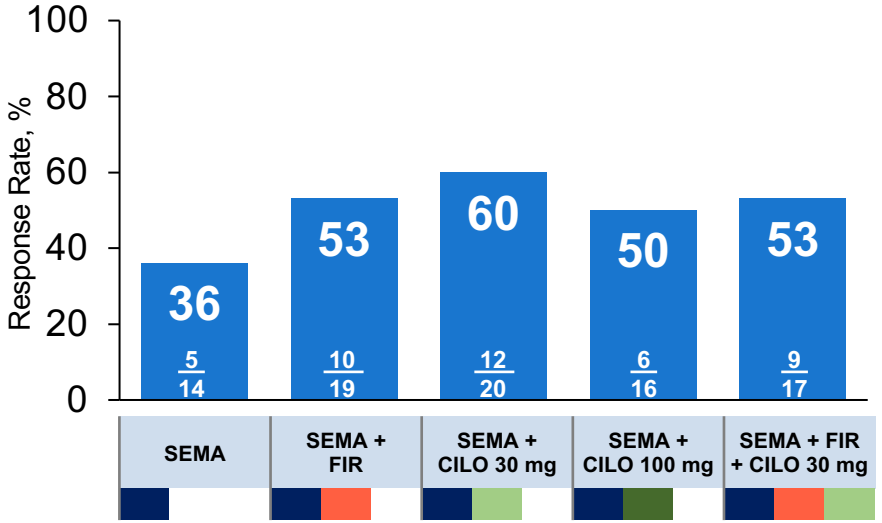
Changes from BL based on ANCOVA models adjusted for BL and diabetes status. * $p<0.05$ vs SEMA alone. ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; BL, baseline; CI, confidence interval; CILO, cilofexor; CK, cytokeratin; ELF, Enhanced Liver Fibrosis score; FIR, firsocostat; GGT, gamma-glutamyl transferase; SEMA, semaglutide.

Reductions in Liver Stiffness by VCTE in All Groups

Absolute Change at Week 24



≥25% Reduction at Week 24[1]



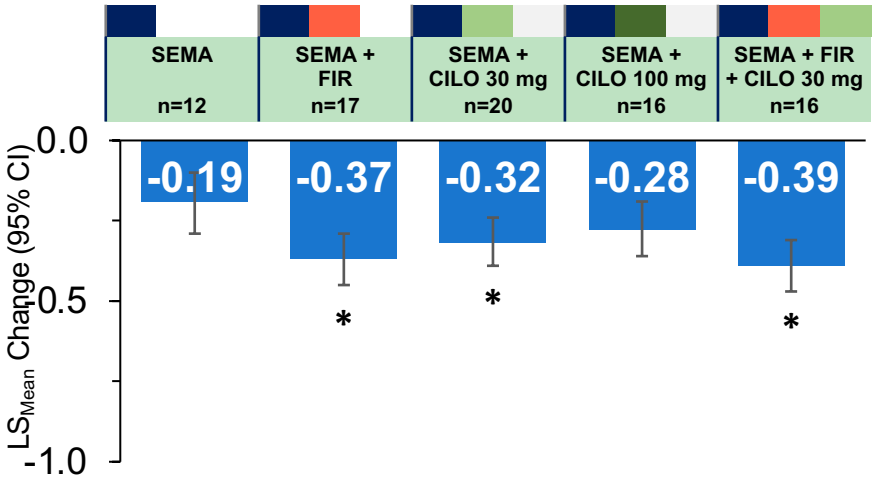
- Similar reductions in LS by VCTE between treatment groups
  - No differences in changes in LS by MRE

Changes in LS by VCTE based on ANCOVA models adjusted for BL and diabetes status. ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; CILO, cilofexor; FIR, firsocostat; LS, liver stiffness; LSmean, least squares mean; MRE, magnetic resonance elastography; SEMA, semaglutide; VCTE, vibration-controlled transient elastography.

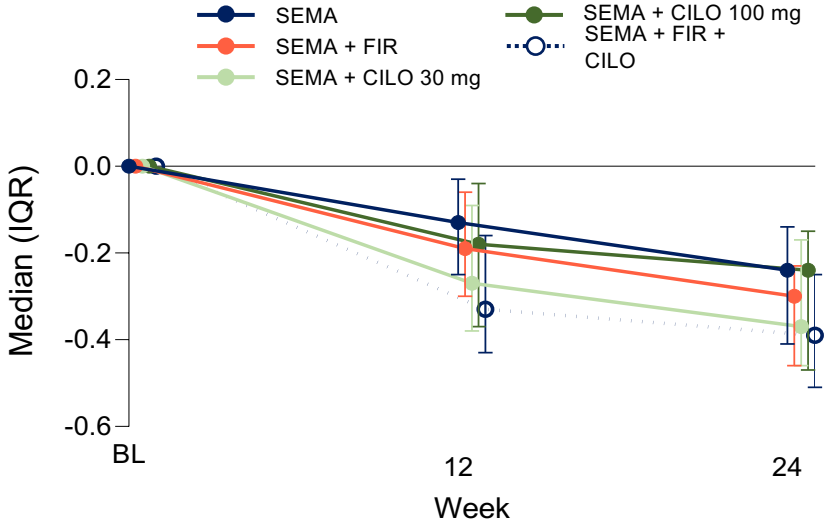
1. Harrison SA, et al. J Hepatol 2020;73:26–39.

FAST Score: Greater Improvements with Combinations

Change at Week 24



Change from Baseline



- All combinations, except CILO + FIR 100 mg, led to significantly greater improvements in FAST score vs SEMA alone

Changes in FAST score based on ANCOVA models adjusted for BL and diabetes status. * p<0.05 vs SEMA alone. ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; CILO, cilofexor; FAST, FibroScan-aspartate aminotransferase; FIR, firsocostat; IQR, interquartile range; LSmean, least squares mean; SEMA, semaglutide.

1. Newsome PN, et al. Lancet Gastroenterol Hepatol 2020;5:362–73.

Similar Improvements in Glycemic Parameters in All Groups

LS_{Mean} (95% CI) change from BL at Week 24	SEMA	SEMA + FIR	SEMA + CILO 30 mg	SEMA + CILO 100 mg	SEMA + FIR + CILO 30 mg
Diabetes patients only	**n=7**	**n=12**	**n=10**	**n=8**	**n=10**
HbA_{1c}, %†	–1.4 (–1.8, –1.0)	–1.7 (–2.0, –1.4)	–1.7 (–2.0, –1.3)	–1.2 (–1.6, –0.8)	–1.4 (–1.8, –1.1)
All patients	**n=16**	**n=18**	**n=20**	**n=17**	**n=17**
HbA_{1c}, %	–1.0 (–1.2, –0.7)	–1.2 (–1.4, –1.0)	–1.1 (–1.3, –0.9)	–1.0 (–1.2, –0.8)	–1.0 (–1.2, –0.8)
Plasma glucose, mg/dL	–31 (–40, –23)	–32 (–40, –23)	–22 (–30, –14)	–18* (–26, –10)	–23 (–31, –14)
Insulin, µIU/mL	–8.5 (–14.6, –2.5)	–8.2 (–13.9, –2.5)	–10.6 (–16.0, –5.2)	–6.3 (–12.1, –0.5)	–4.6 (–10.6, 1.5)
HOMA-IR	–3.5 (–5.3, –1.7)	–3.8 (–5.5, –2.1)	–3.9 (–5.5, –2.2)	–2.3 (–4.1, –0.6)	–2.5 (–4.3, –0.7)

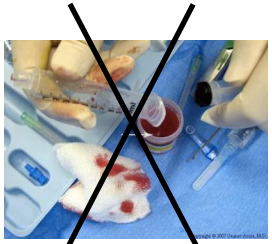
Changes in glycemic parameters based on ANCOVA models adjusted for BL and diabetes status.
* $p<0.05$ vs SEMA alone. † Changes in HbA_{1c} in patients with diabetes based on ANCOVA models adjusted for BL value.
ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; CILO, cilofexor; FIR, firsocostat; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; LSmean, least squares mean; SEMA, semaglutide.

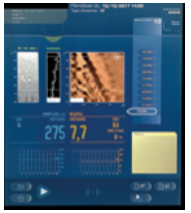
Conclusion: The Future is Bright!

- **Natural History**
- **Diagnostics**
- **Therapeutics**

Cirrhosis regression &others

Menu of Options





Many successful stories

“There is no elevator to success,

you have to take the stairs”