“Recent NASH Clinical Trial Results and Implications” 2020

#2 Gastroenterology

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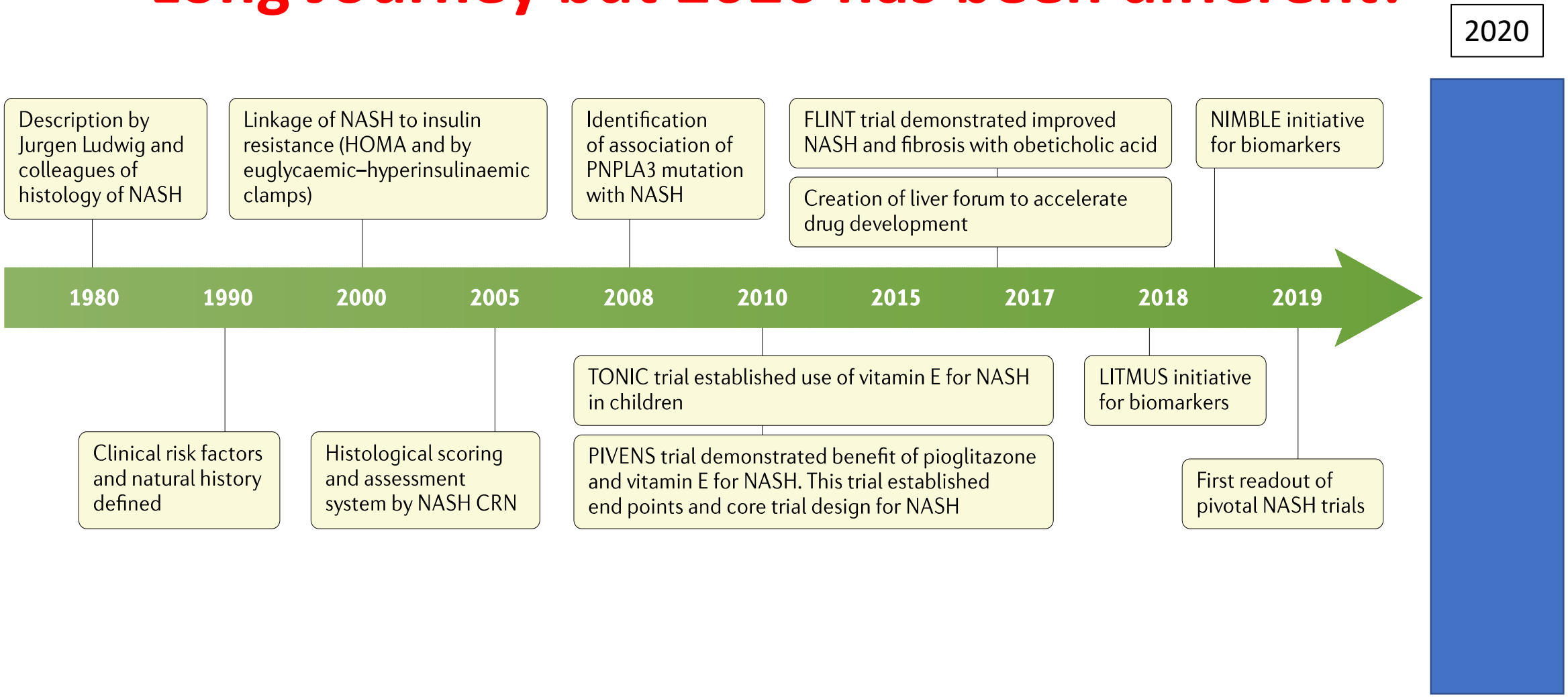
Disclosures

- MN has been on the advisory board for Gilead, Intercept, Pfizer, Novartis, Allergan, Fractyl, Blade, EchoSens North America, OWL, Siemens, and Abbott; MN has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Novartis, Shire and Zydus; MN is a minor shareholder or has stocks in Anaetos and Viking. SEP

Long Journey but 2020 has been different!



Sanyal AJ; Nature Rev Gastro & Hep 2019

FDA Efficacy Endpoints for Phase 3 Trials: Liver Histologic Improvement

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

and

- No worsening of liver fibrosis

Fibrosis Improvement

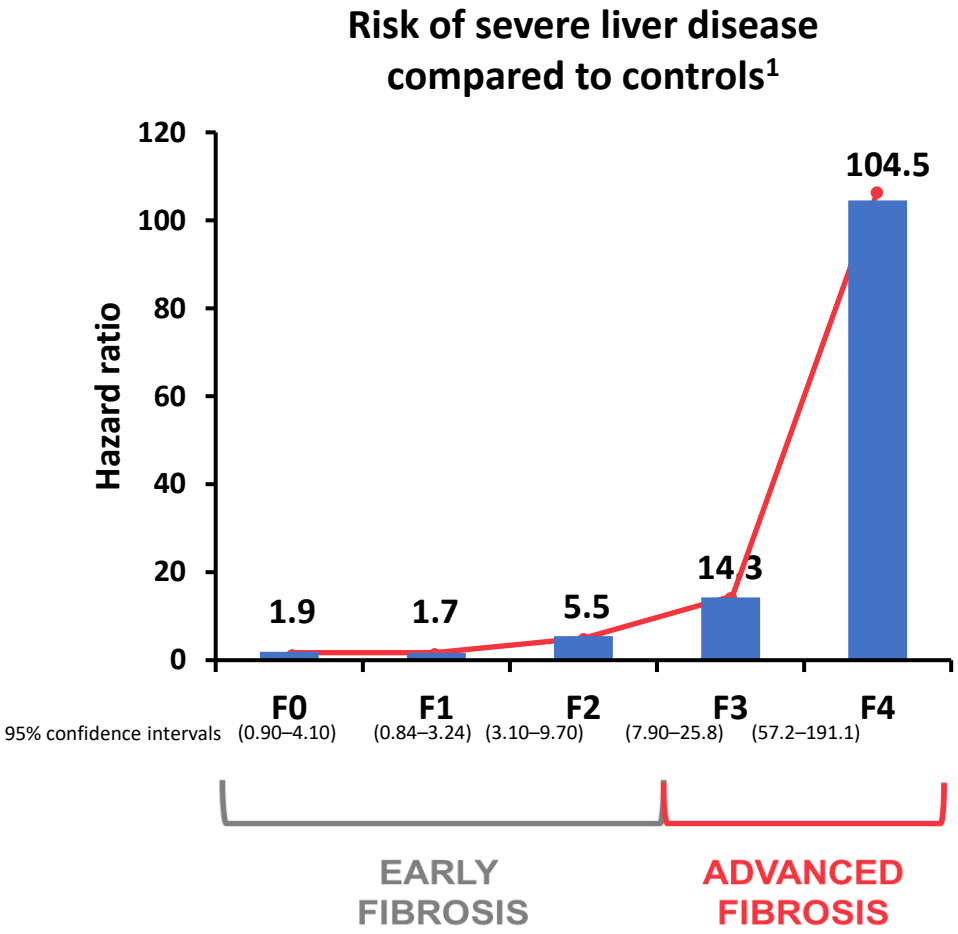
- Improvement ≥ 1 fibrosis stage

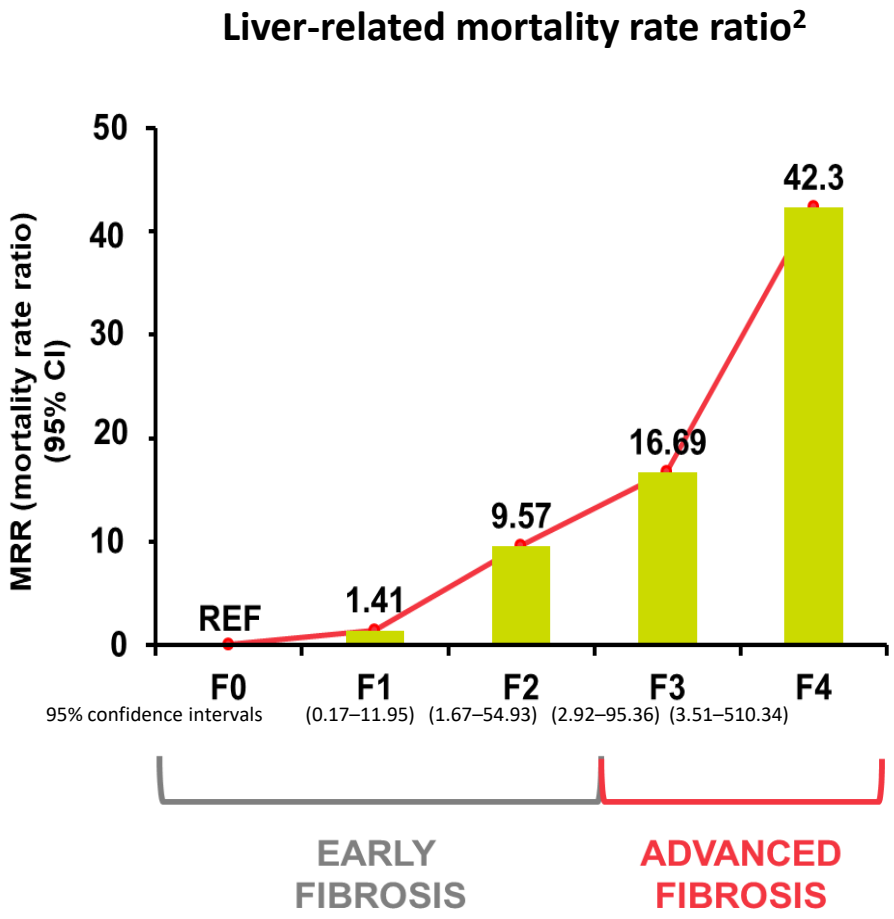
and

- No worsening of steatohepatitis

US FDA. Draft Guidance. Noncirrhotic NASH With Liver Fibrosis. December 2018.

Significant Fibrosis increases the risk of liver-related morbidity and mortality





1. Hagström H et al. *J Hepatol* 2017;67:1265 –1273; 2. Dulai PS et al. *Hepatology* 2017;65(5):1557–1565.

Efficacy Endpoints for Early Phase 2 Trials

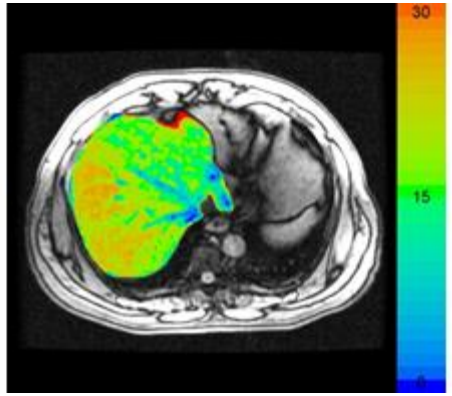
Liver Fat Fraction (MRI-PDFF)

- ≥ 5% absolute/ ≥ 30% relative reduction associated with improvement in NAFLD activity score without fibrosis worsening[2]

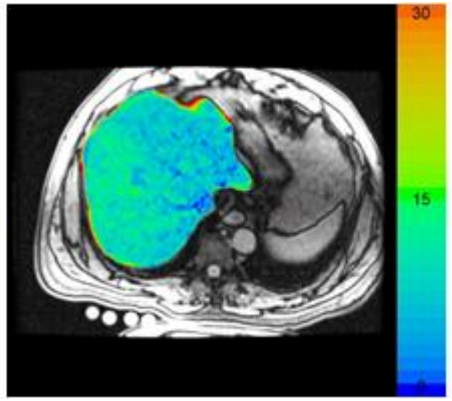
ALT

- Reduction in ALT associated with histologic improvement or resolution of NASH[1]

Baseline fat fraction 18.8%

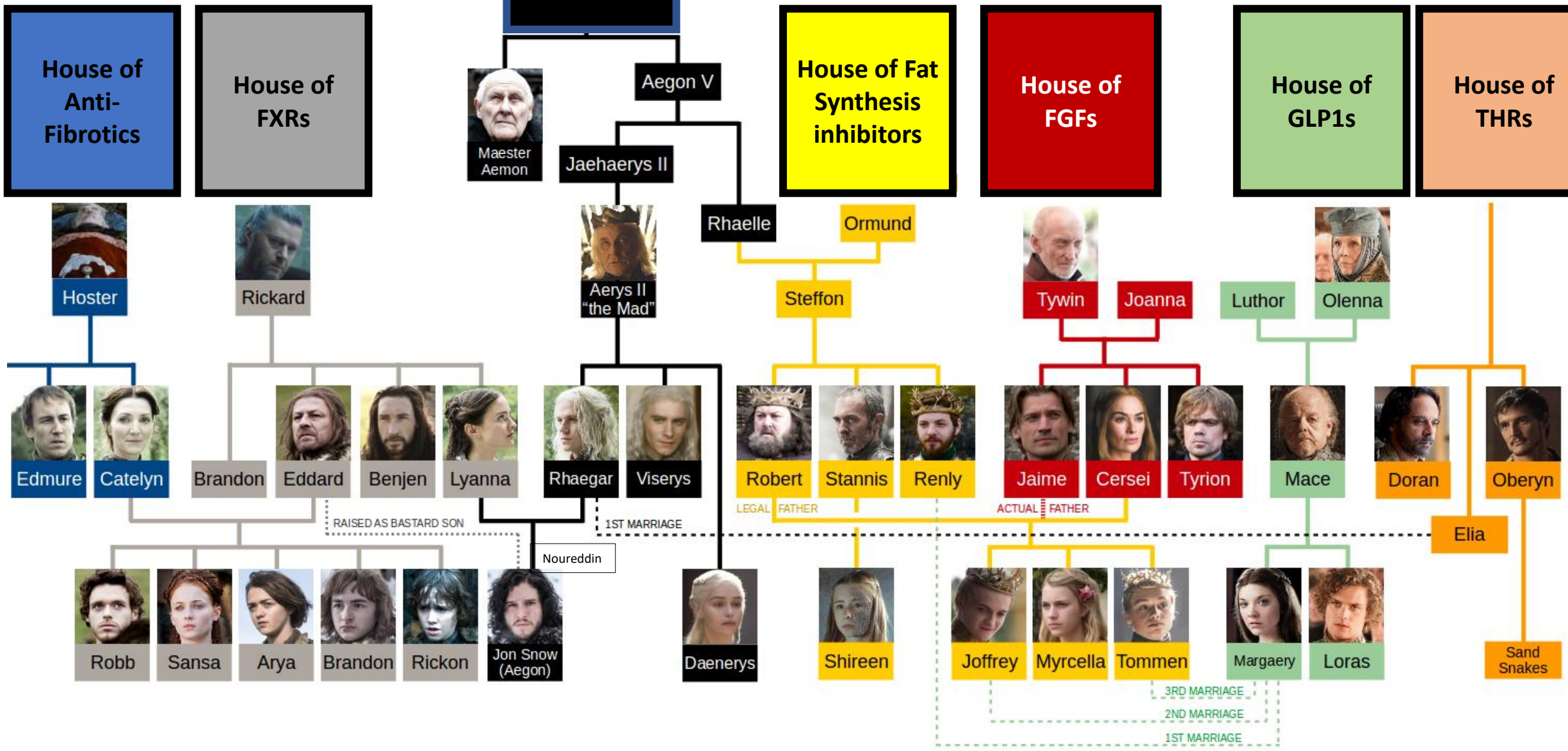


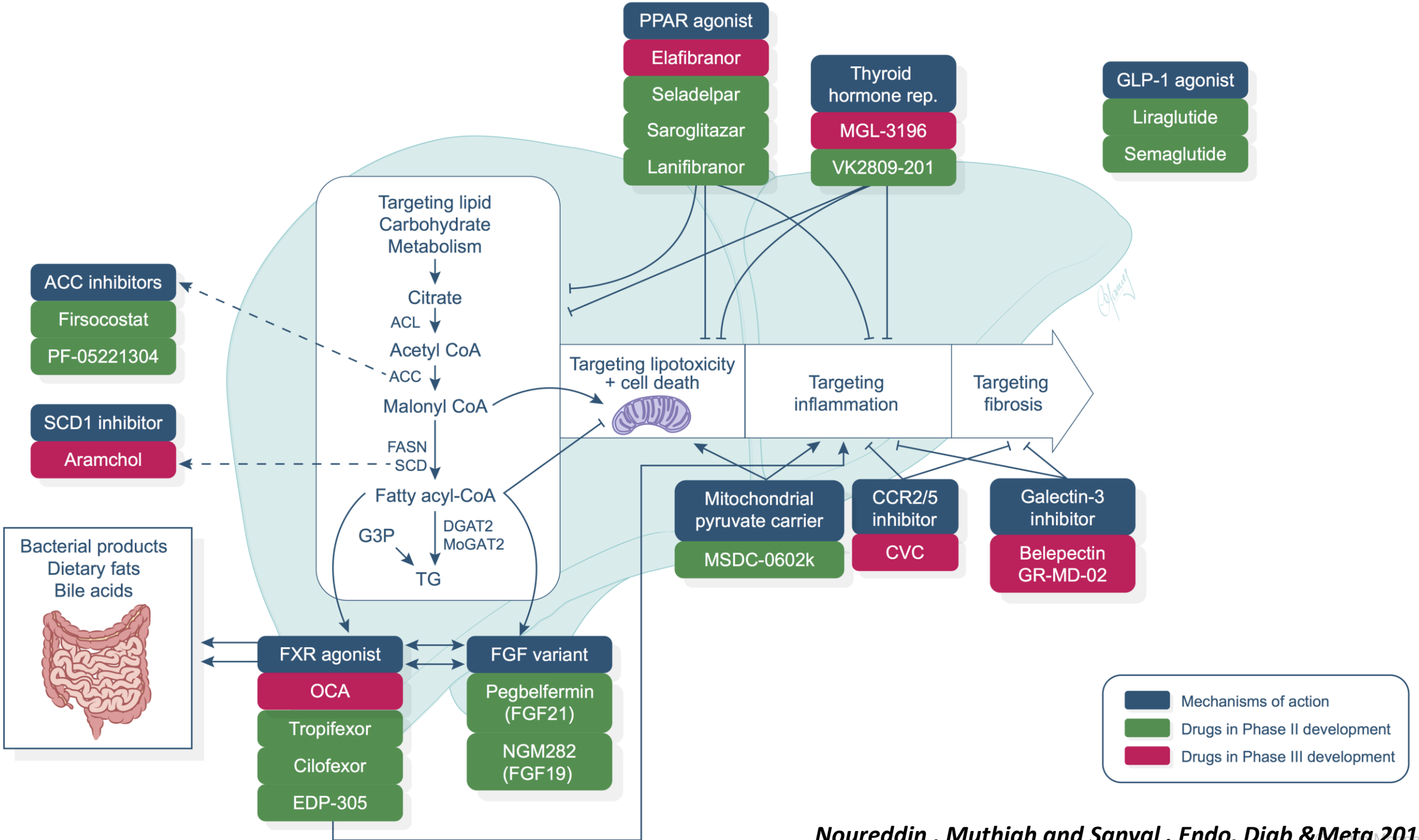
Week 16 fat fraction 8.3%



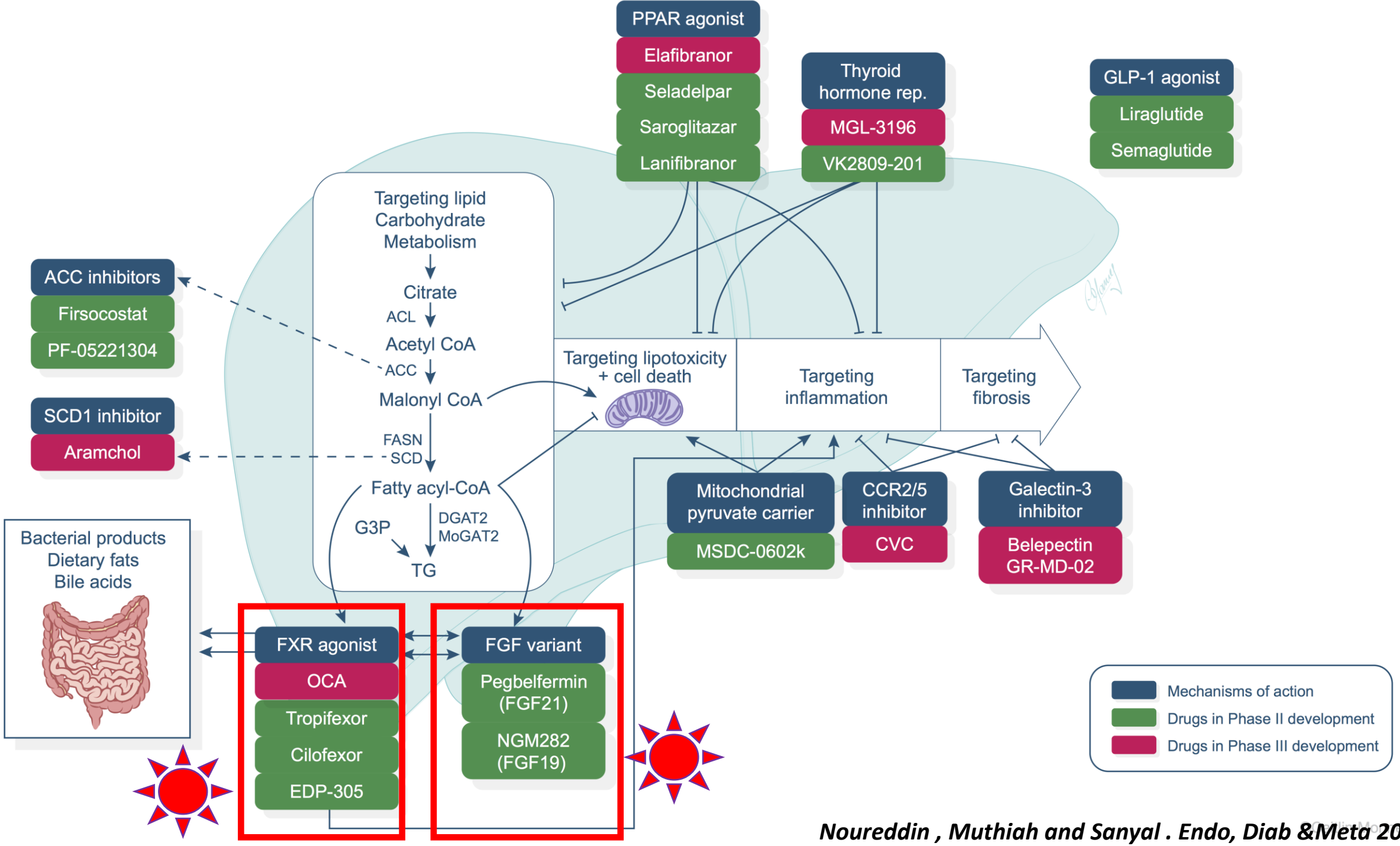
Vuppalanchi. Clin Gastroenterol Hepatol. 2014;12:2121.
Patel. Therap Adv Gastro 2016;9:692.

GAME OF NASH DRUGS



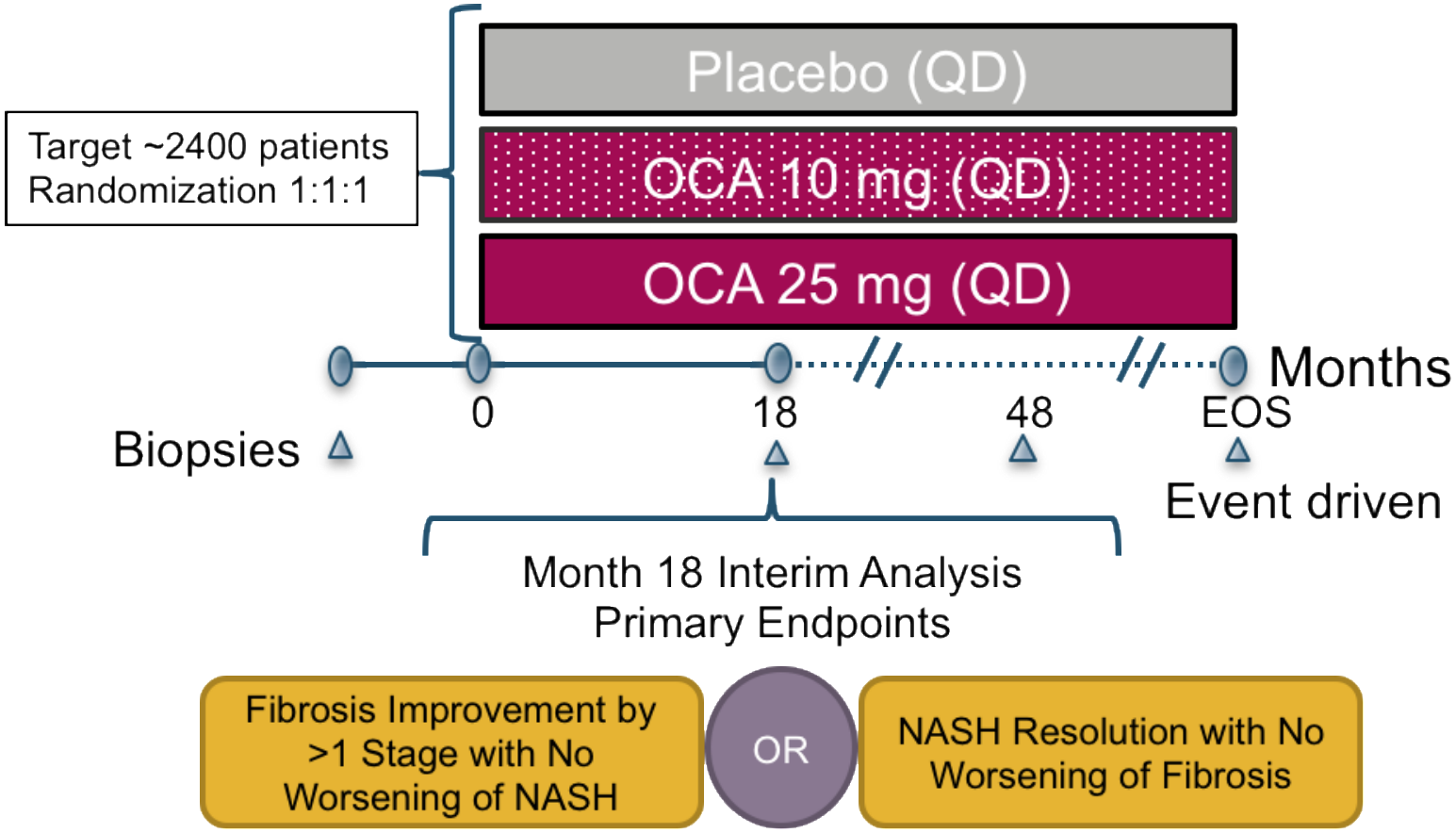


Noureddin , Muthiah and Sanyal . Endo, Diab &Meta 2019



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

Obeticholic Acid: REGENERATE Design

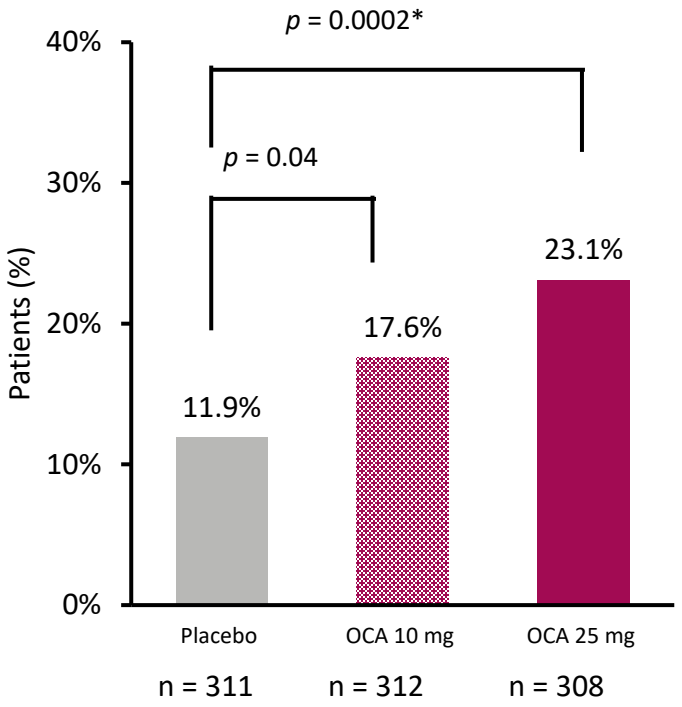


Study success was defined as achievement of one of the 2 primary endpoints

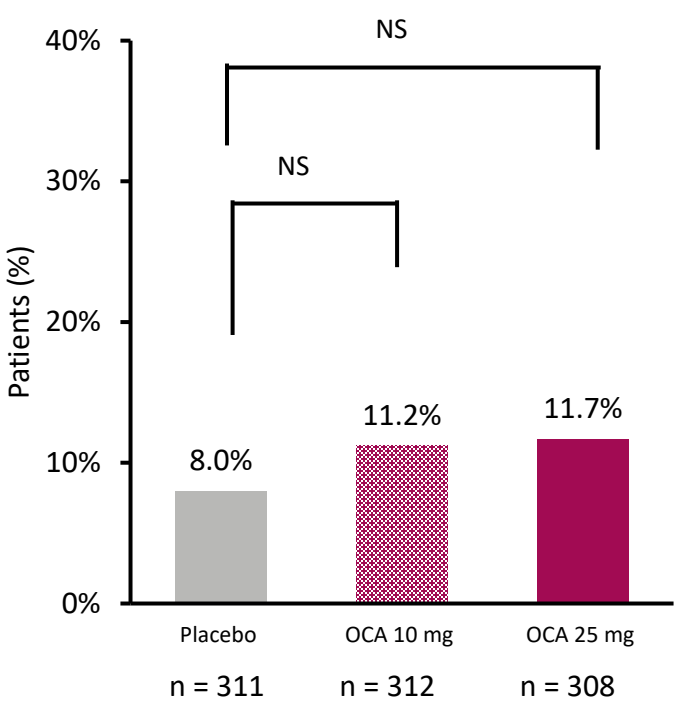
Ratziu V et al; Contemp Clini Trials 2019
Younossi Z, et al; Lancet 2020.

Obeticholic Acid: REGENERATE Results

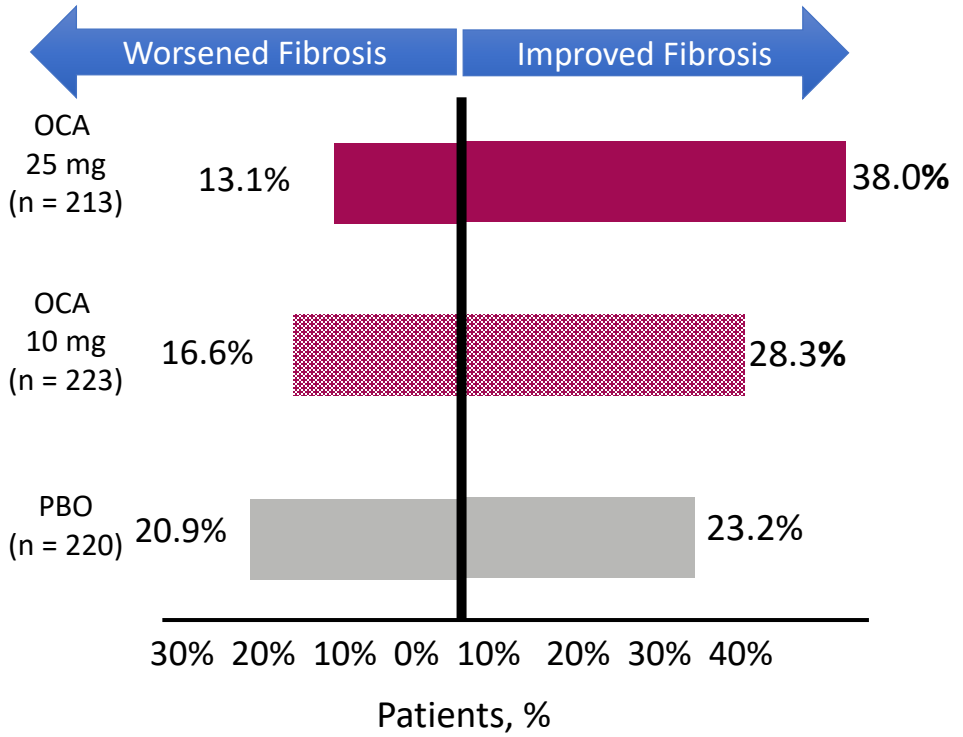
Primary Endpoint (ITT): Fibrosis Improvement by ≥1 Stage With No Worsening of NASH



NASH Resolution With No Worsening of Liver Fibrosis

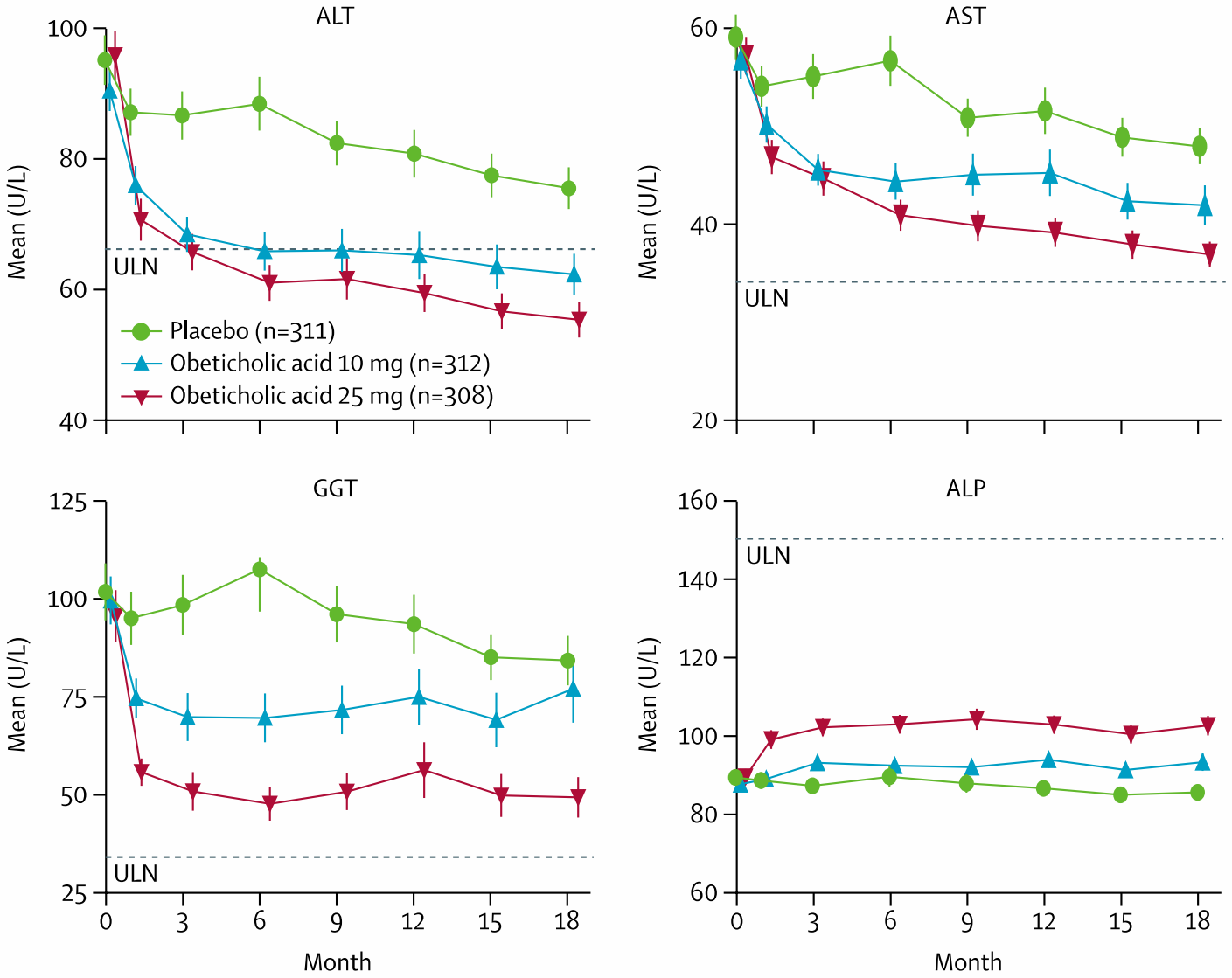


Regression or Progression of Fibrosis by ≥1 Stage (Per Protocol With Post-Baseline Biopsy)



Ratziu V et al; Contemp Clini Trials 2019
Younossi Z, et al; Lancet 2020.

REGENERATE Study:
Obeticholic Acid in NASH Patients Without Cirrhosis



SE:
Lipid changes
Itching

Younossi et al Lancet 2019

Tropifexor, FXR agonist, REDUCES hepatic fat and ALT in fibrotic NASH IN 12 weeks: FLIGHT-FXR Part C interim results

Objective: Assess safety, tolerability, and efficacy of several doses of tropifexor (TXR) in NASH

Methods: Phase 2 RDBPC, 3-part study

- Parts A&B previously presented
- Part C (48W) TXR 140 µg and 200 µg doses on biomarkers and histology in biopsy-proven NASH F2-3; 12W interim results presented here

Main Findings: TXR associated with dose-dependent decreases in ALT, GGT, weight & HFF

AE: SAE frequency similar across groups; 2-6% DC due to pruritus; no DC for LDL increases

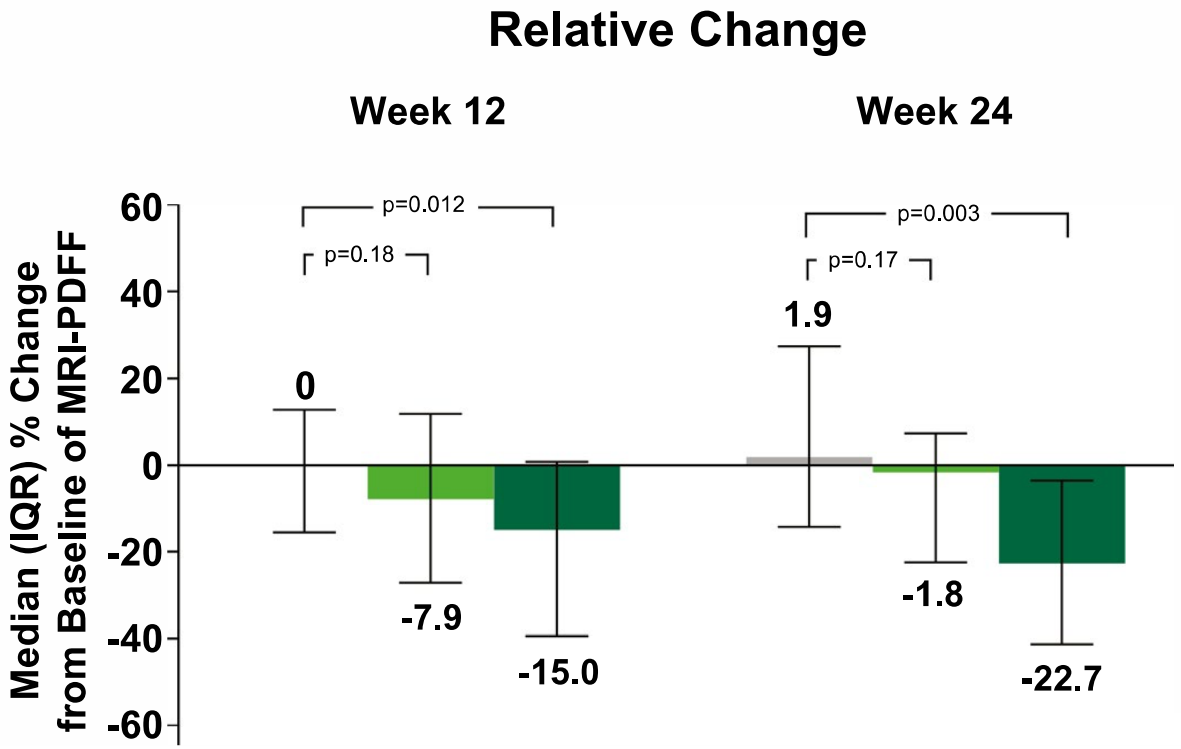
Conclusions: Positive 12 Week/Interim Result

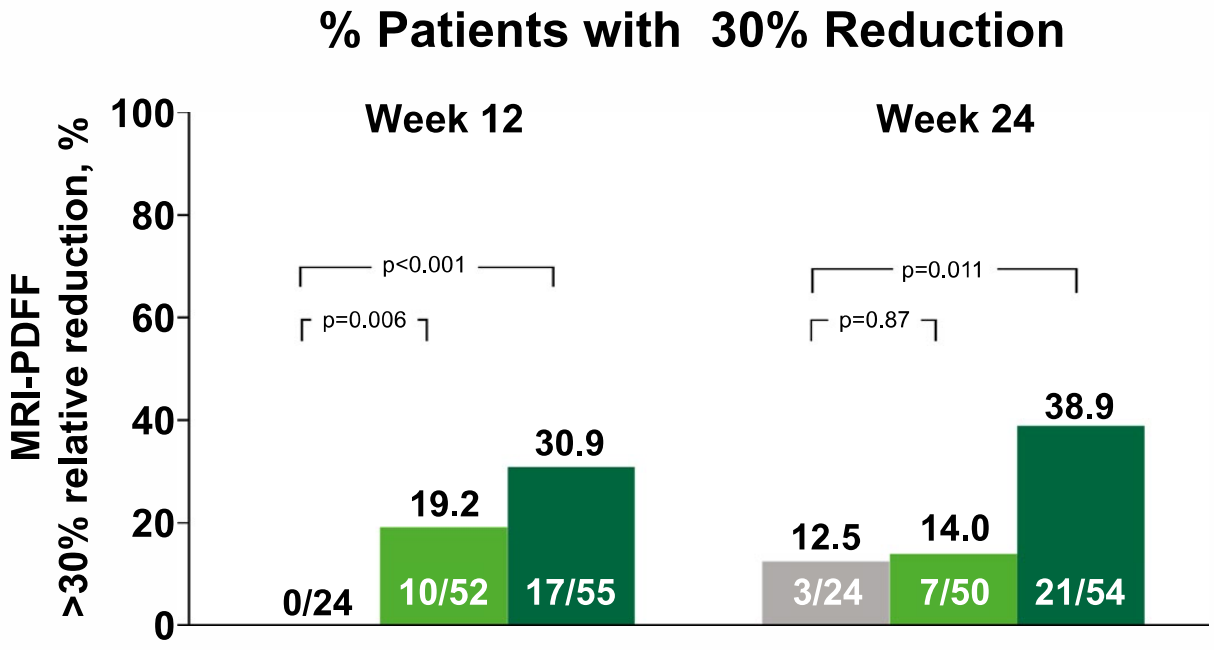
Table: LS means of absolute changes in ALT, GGT, and body weight, and relative change in hepatic fat fraction (HFF) from baseline to W12

Biomarkers	Placebo (N=51)	TXR 140 µg (N=50)	TXR 200 µg (N = 51)
ALT (U/L)	−8.9 (4.19) n = 49	−20.1 (4.57) n = 41; *P* = 0.058	−23.6 (4.48) n = 39; *P* = 0.013
Relative change in HFF* (%)	−10.26 (4.21) n = 51	−16.99 (4.64) n = 49; *P* = 0.209	−31.37 (4.30) n = 51; *P*<0.001
GGT (U/L)	−2.5 (3.55) n = 49	−39.2 (3.70) n = 44; *P*<0.001	−40.9 (3.62) n = 46; *P*<0.001
Body weight (kg)	−1.14 (0.36) n = 50	−2.46 (0.38) n = 46; *P* = 0.010	−3.20 (0.37) n = 46; *P*<0.001

Sanyal A, et al; AASLD 2019 Abstract 17970 (L04)

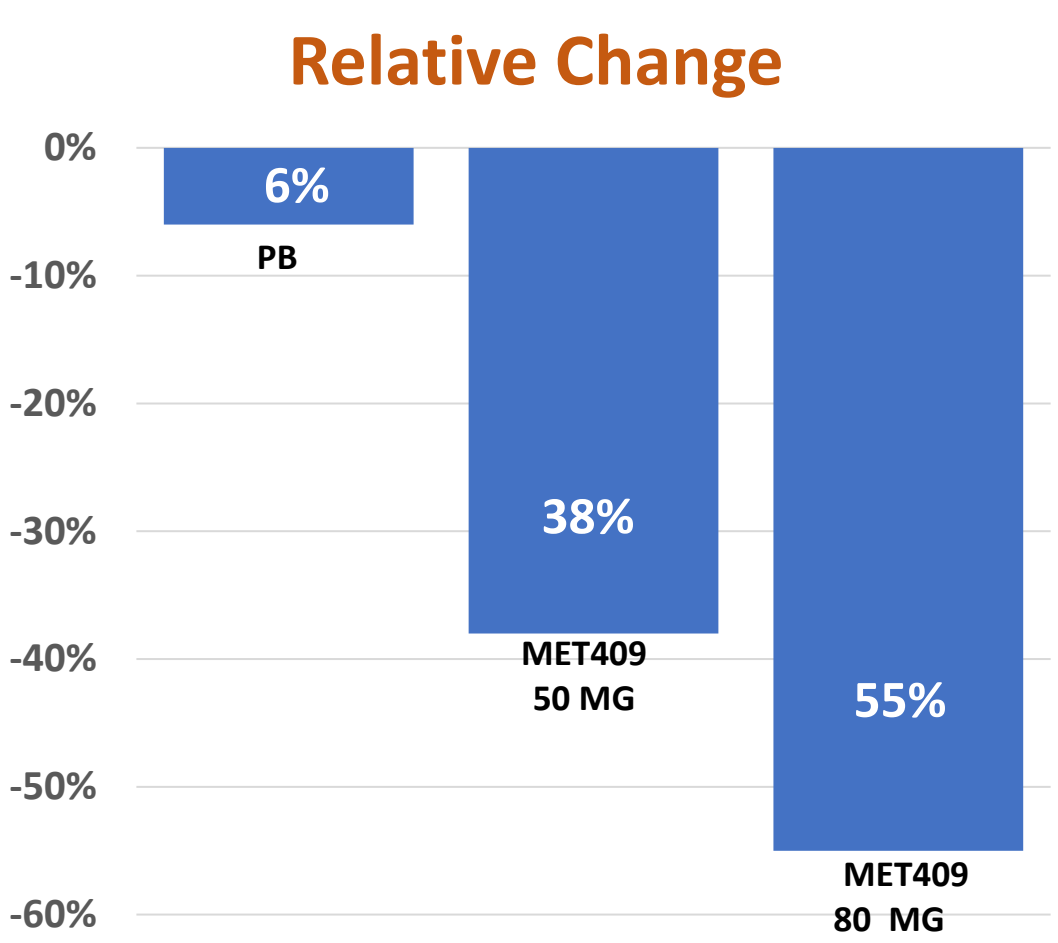
Cilofexor, a Nonsteroidal FXR Agonist, in Patients With Noncirrhotic NASH: A Phase 2 Randomized Controlled Trial

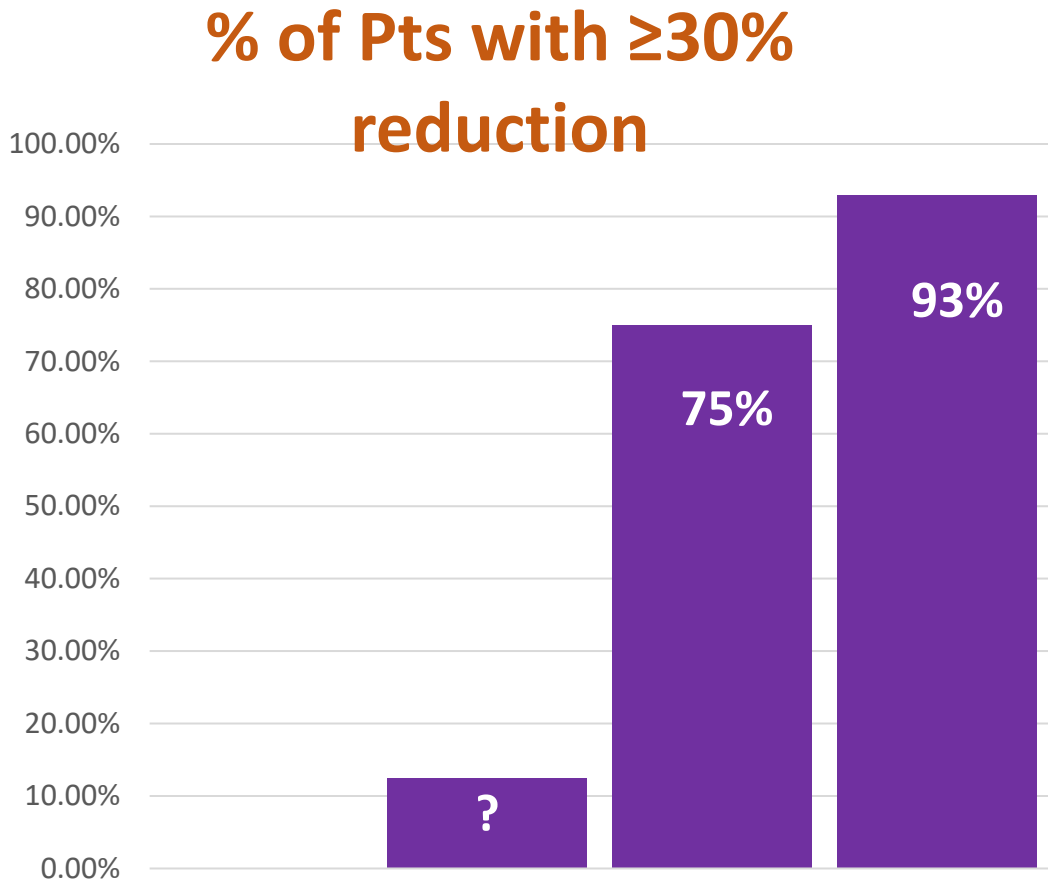




Patel K et al; Hepatology July 2020

Randomized, placebo-controlled 12-week study of MET409 in NAFLD/NASH patients

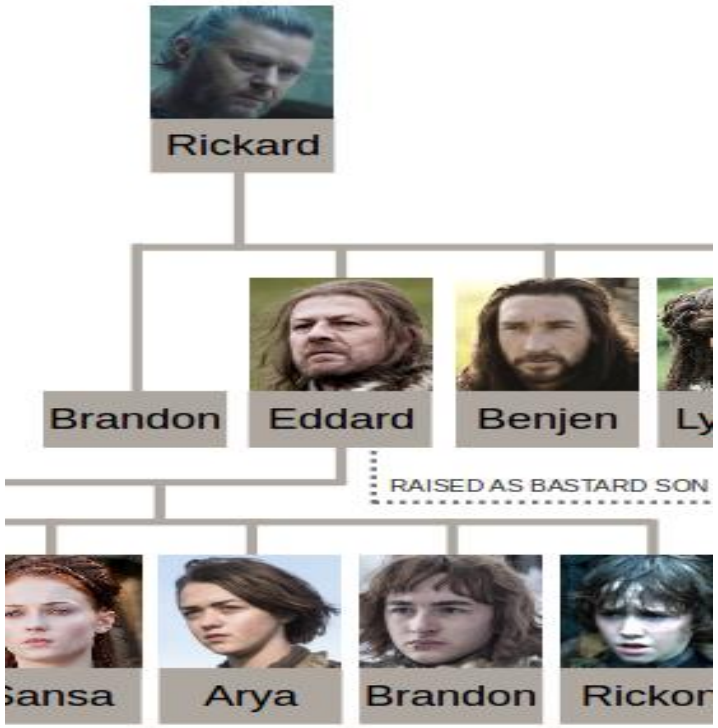




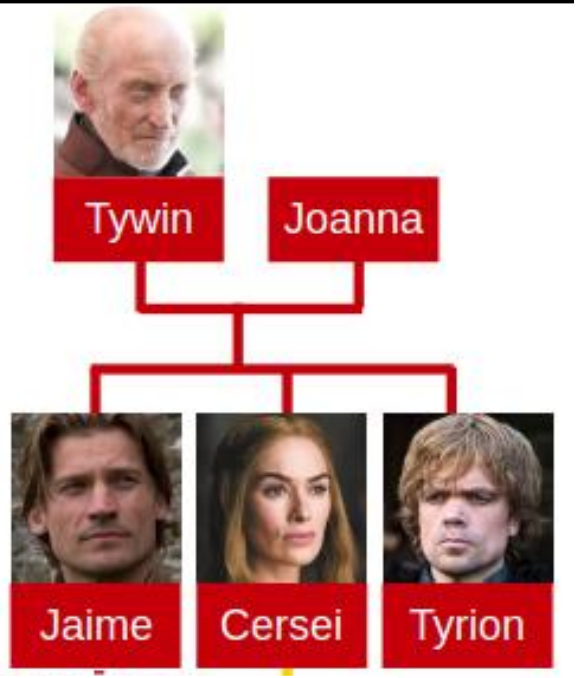
Overall pruritus rates (10-35%)

Source: Press release

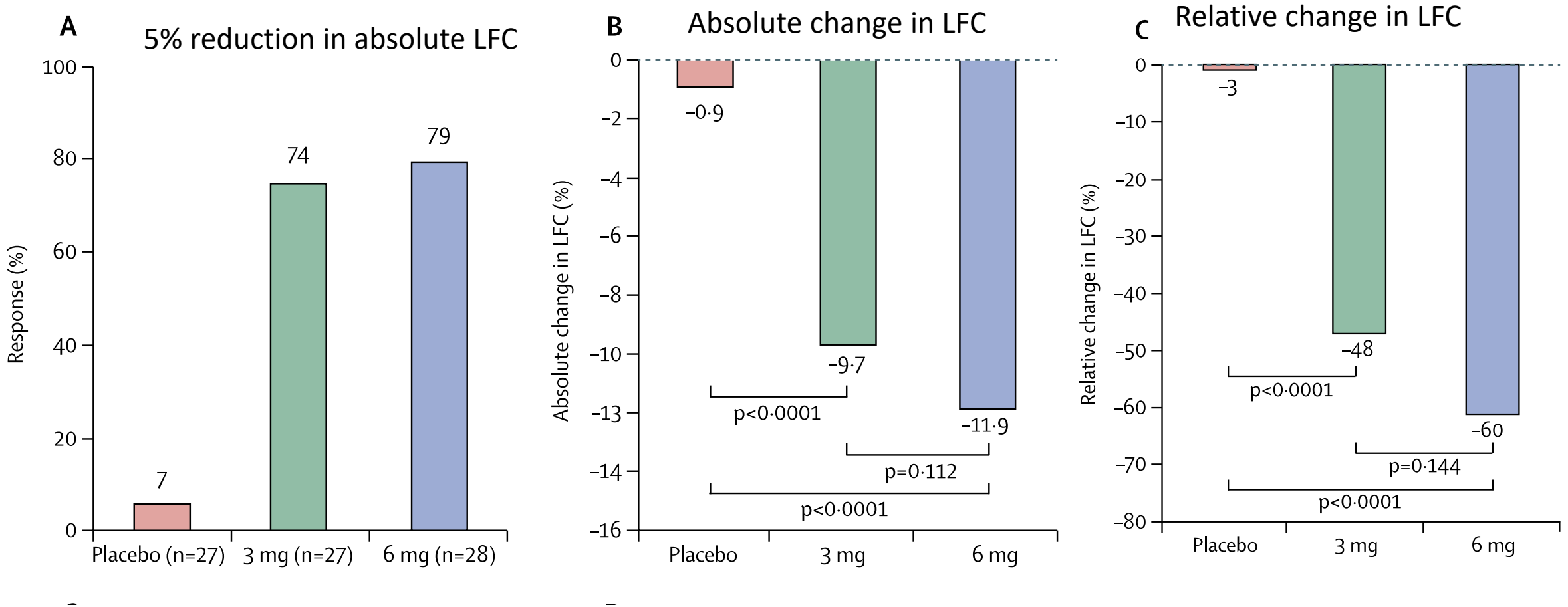
House of FXRs



House of FGFs

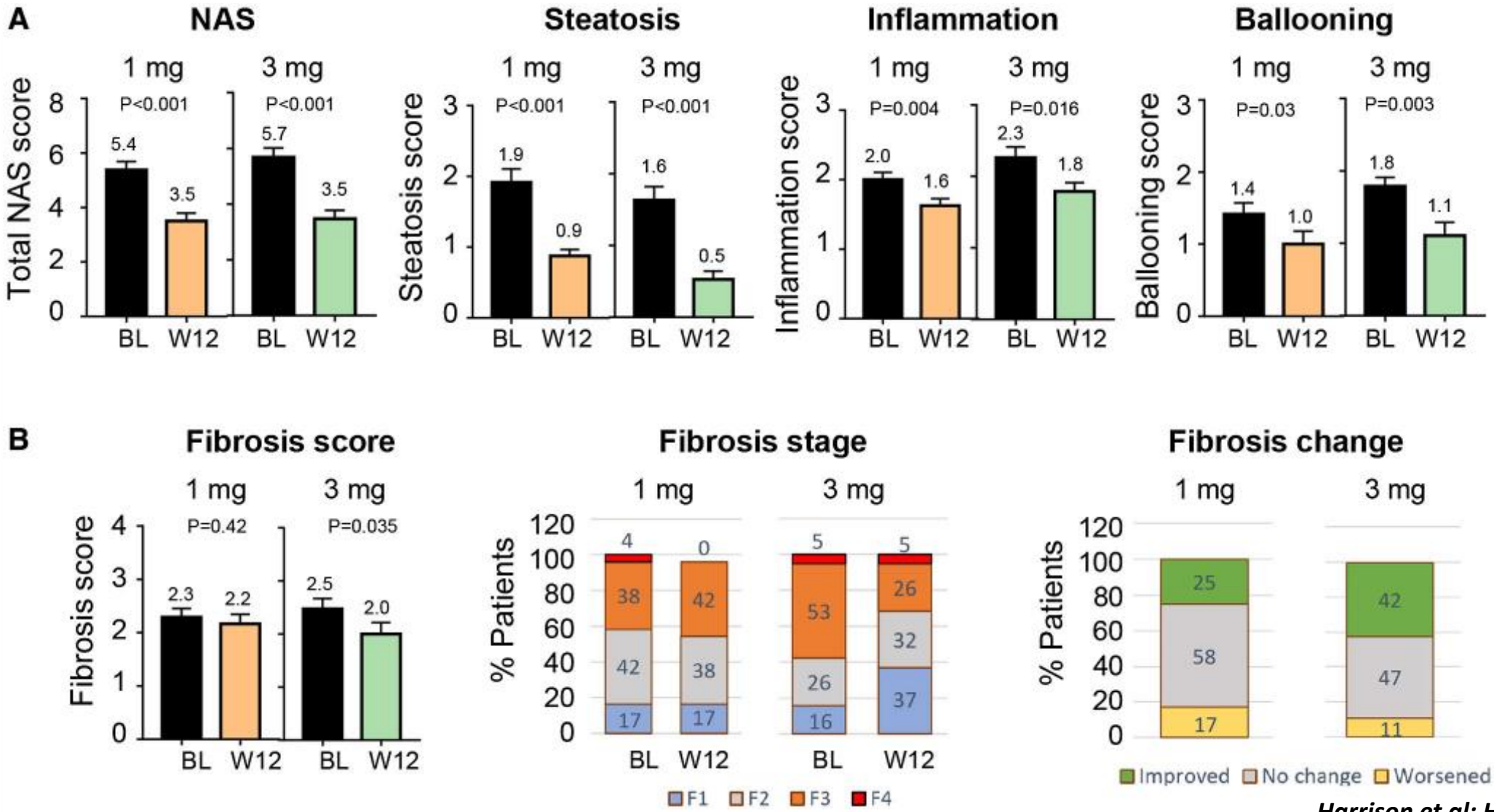


NGM282 (FGF 19) for treatment of NASH: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial (12 weeks)



Harrison S et al; The Lancet 2018

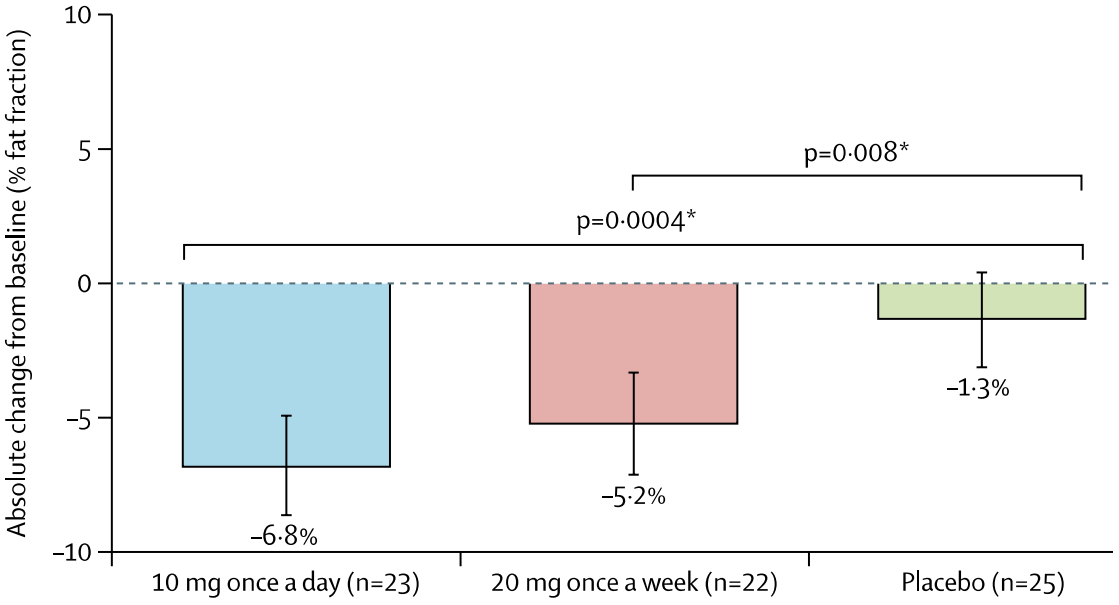
NGM282 Improves Liver Fibrosis and Histology in 12 Weeks in Patients With NASH

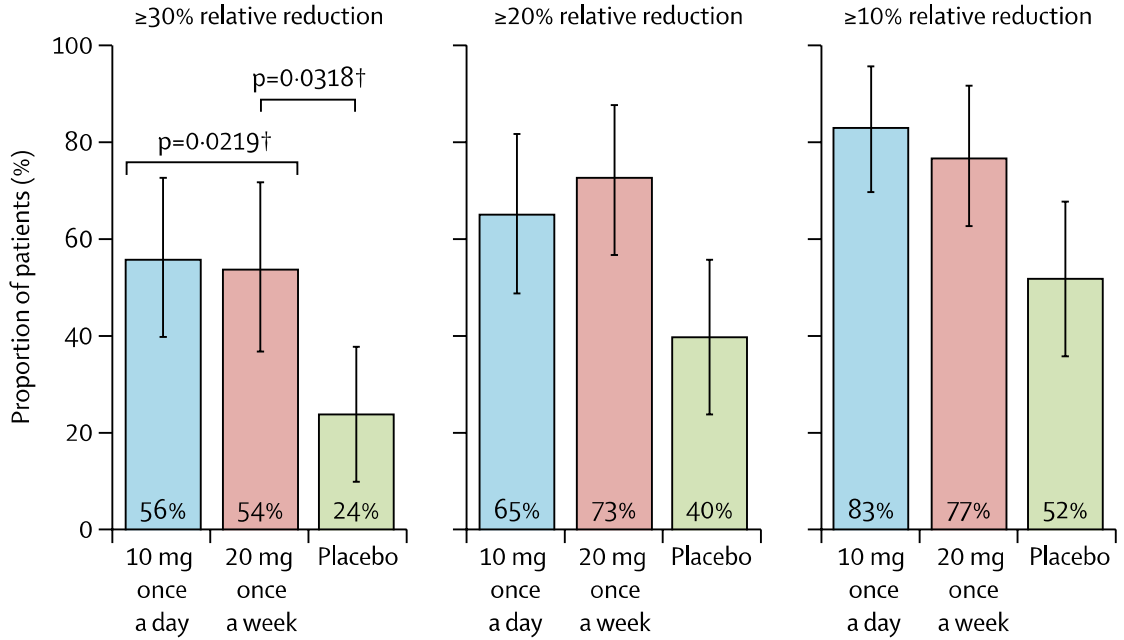


Harrison et al; Hep 2020

Pegbelfermin (BMS-986036), a PEGylated FGF 21 analogue, in patients with NASH: a randomized, double-blind, placebo-controlled, phase 2a trial (16 weeks)

Adjusted mean absolute change in hepatic fat fraction





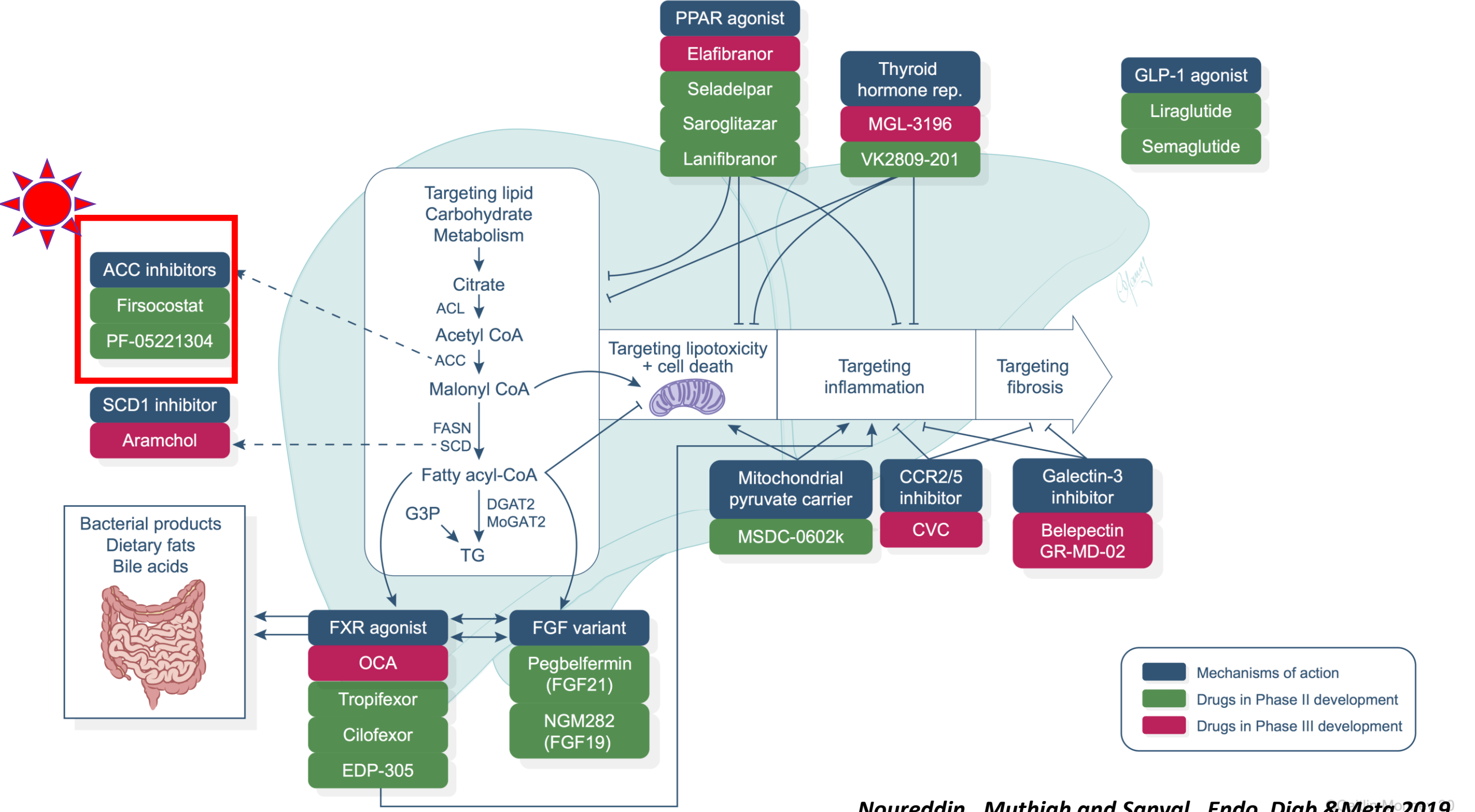
Sanyal et al; The Lancet 2019

Efruxifermin in 16-Week Phase 2a BALANCED Study in NASH Patients

		AKR-001 (once weekly dose)		
Measure (Mean)	Placebo (N=21)	28 mg (N=19)	50 mg (N=20)	70 mg (N=20)
Absolute reduction in liver fat (%)	-0.3	-12.3***	-13.4***	-14.1***
Relative reduction in liver fat (%)	0%	-63***	-71***	-72***
≥30% relative reduction in fat (%)	10	84***	85***	75***
Reduction in ALT (U/L)	-6	-24***	-30***	-32***

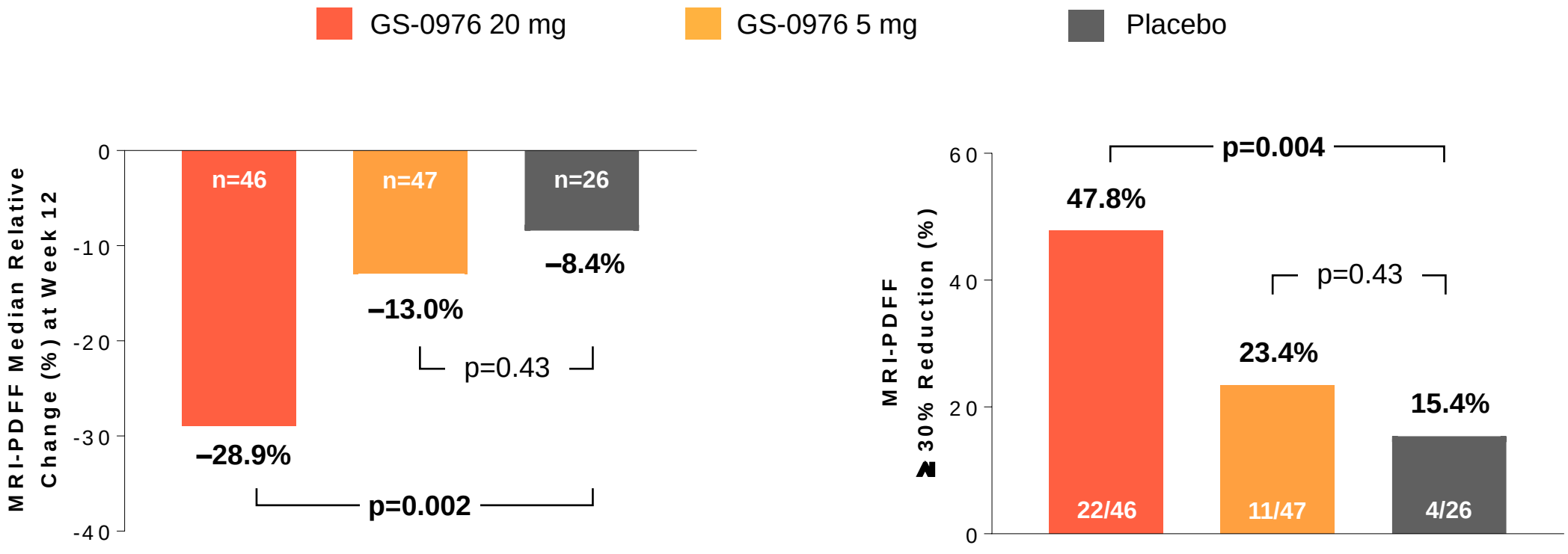
Histology Data was also released in a press release but was only in sub-group and was not powered

Source : Press Release



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

Firosocostat GS-0976 : 12 –weeks Randomized placebo-controlled trial of patients with NAFD/NASH



- GS-0976 20 mg resulted in a clinically significant[1,2] reduction in MRI-PDFF

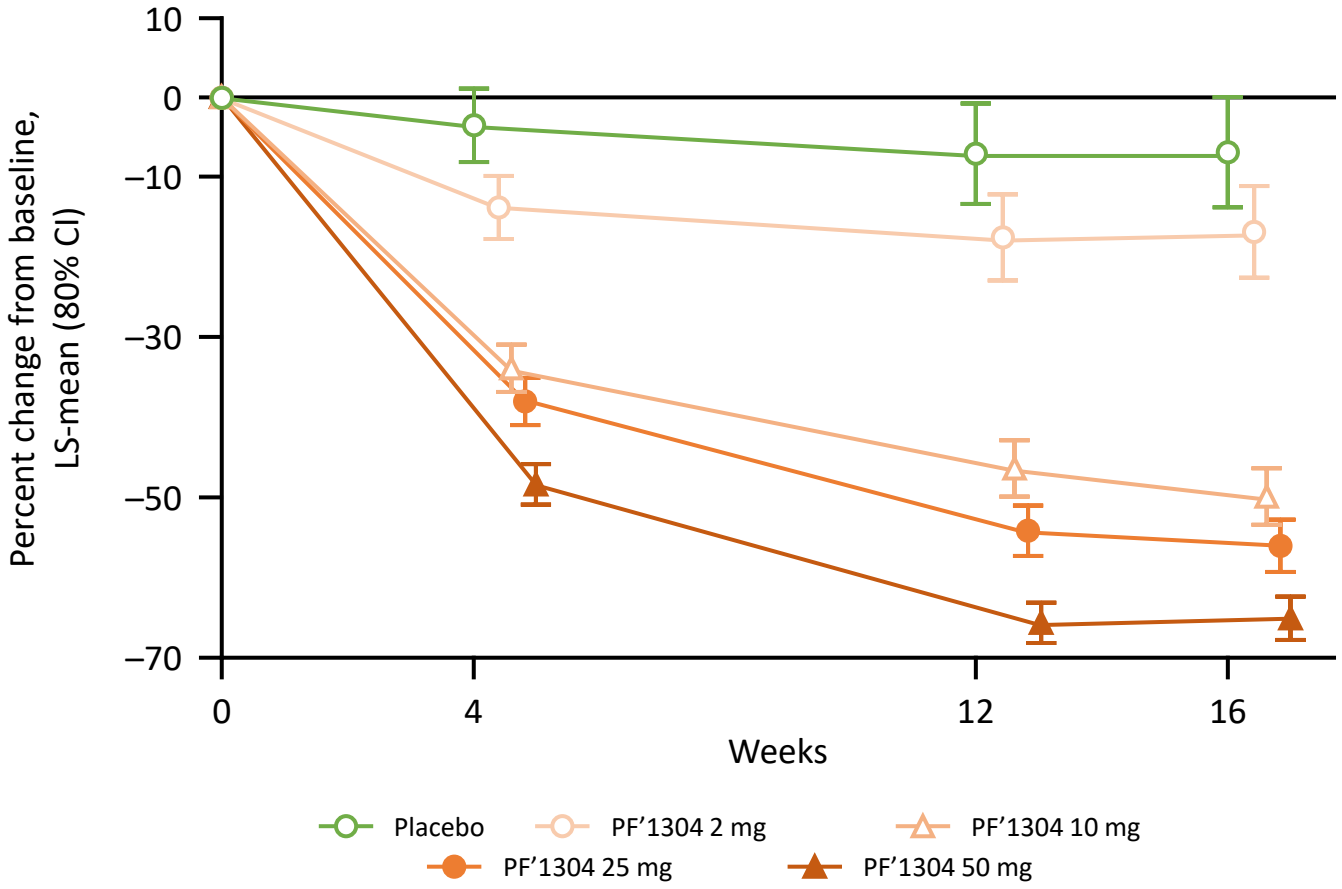
- p-values for change in MRI-PDFF at Week 12 by Wilcoxon rank-sum test.
- p-values for proportion of subjects with ≥30% reduction in MRI-PDFF by Mantel-Haenszel test with adjustment for diabetes status.
- 1. Patel J, et al. Therap Adv Gastroenterol 2016;9:692-701; 2. Loomba R, et al. AASLD 2017. Abstr 2169

Loomba et al Gastro 2018

Phase 2a, Dose-Ranging Study of PF'1304

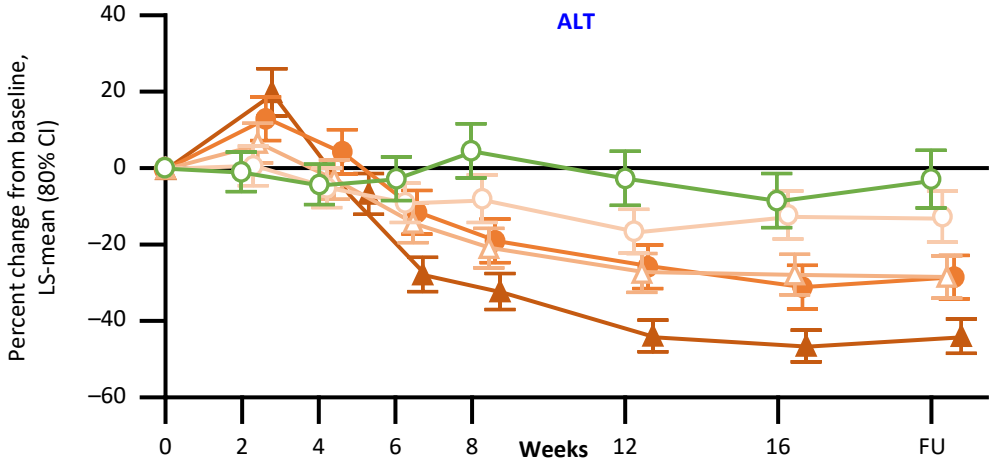
- Reduction in percentage liver fat (MRI-PDFF) *starting at Week 4* and continuing to Week 16 with separation from placebo at top three doses

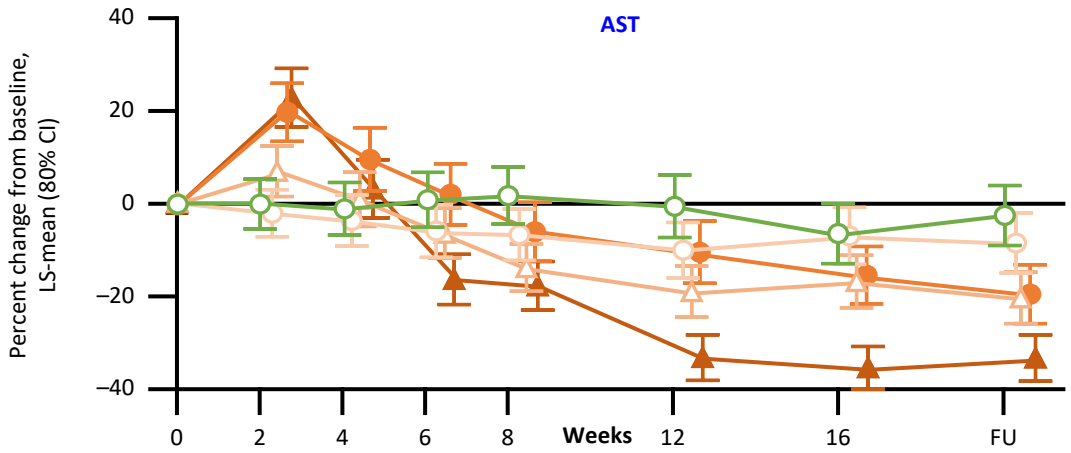
- Proportion of patients who achieve *relative reductions ≥30% at Week 16*:
  - Placebo, 6%
  - PF'1304 2 mg QD, 22%
  - PF'1304 10 mg QD, 74%
  - PF'1304 25 mg QD, 87%
  - PF'1304 50 mg QD, 90%

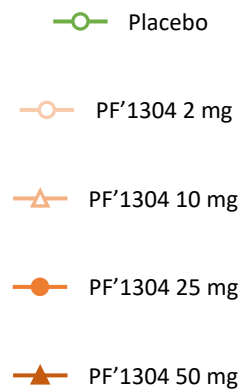


Amin et al; AASLD 2019

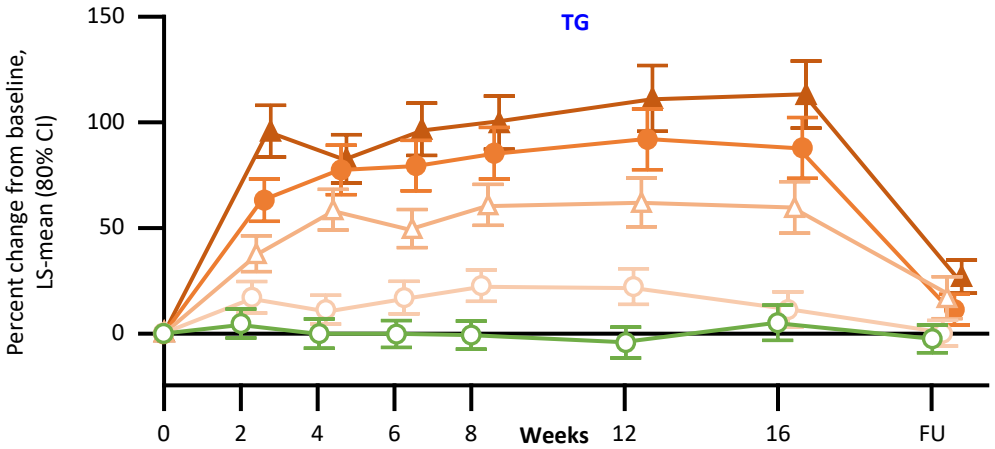
Changes in Liver Function Tests Over Time

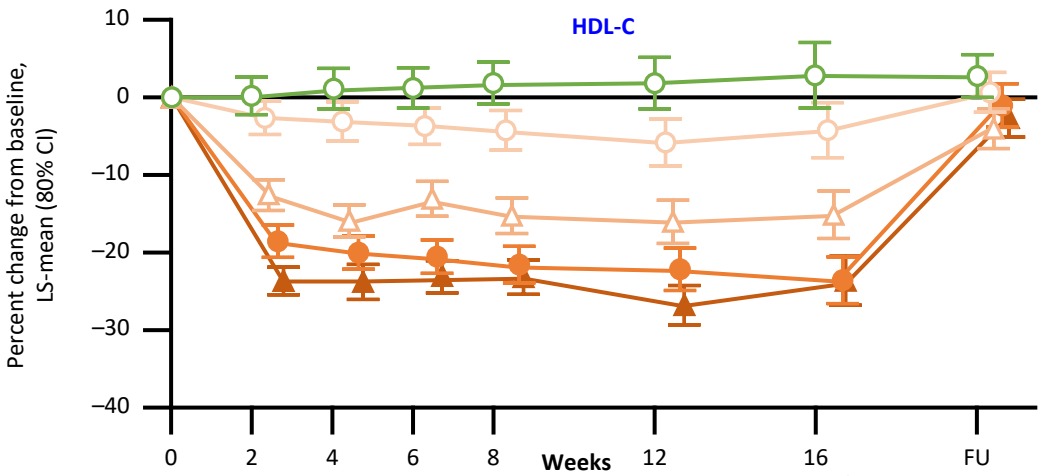




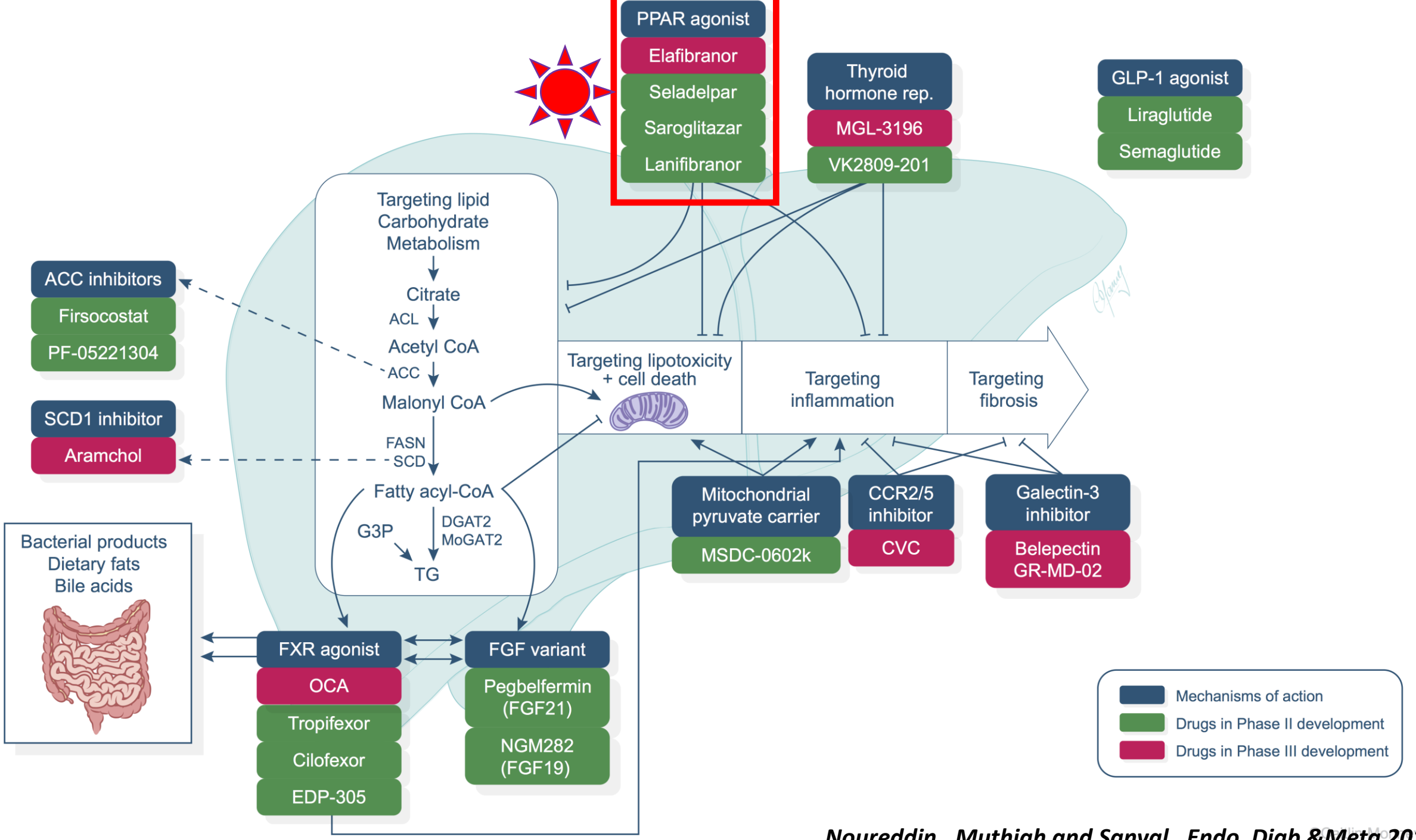


Changes in Fasting Lipid Panel Over Time



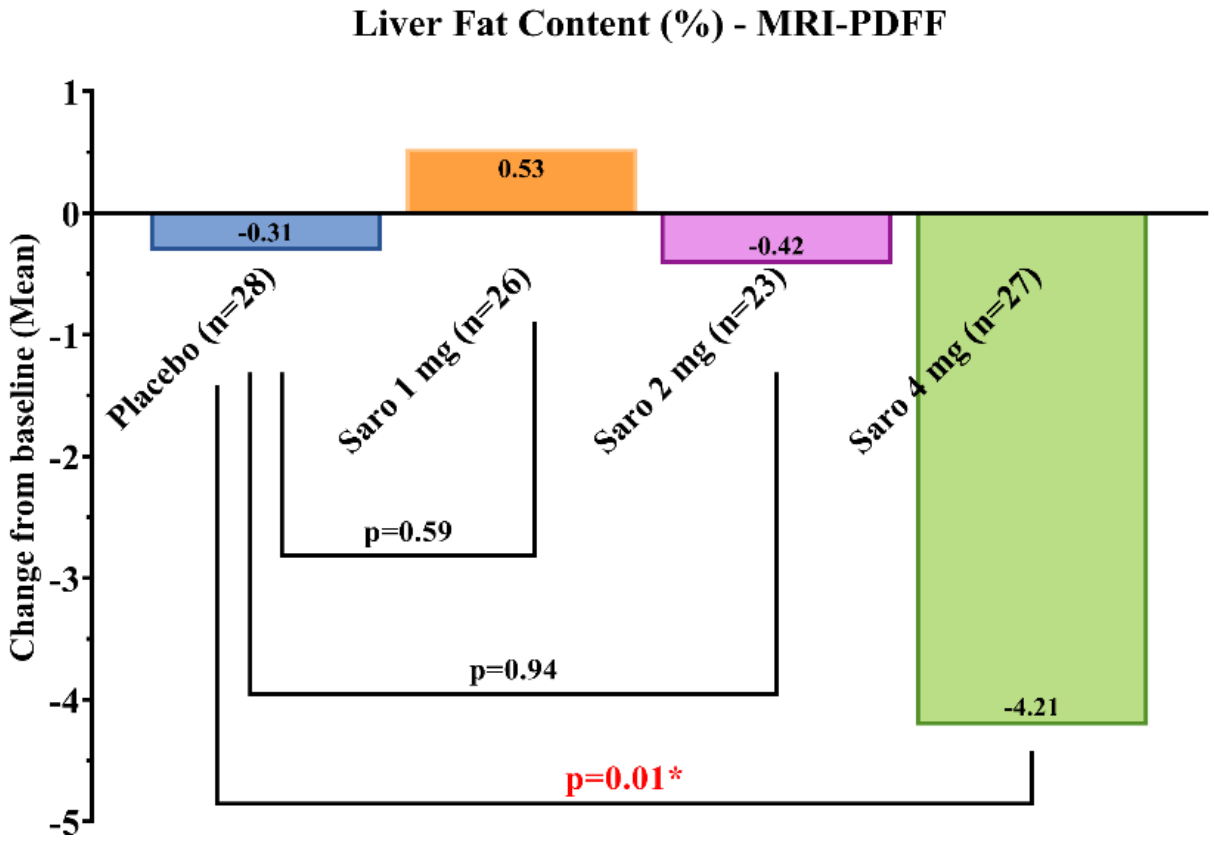


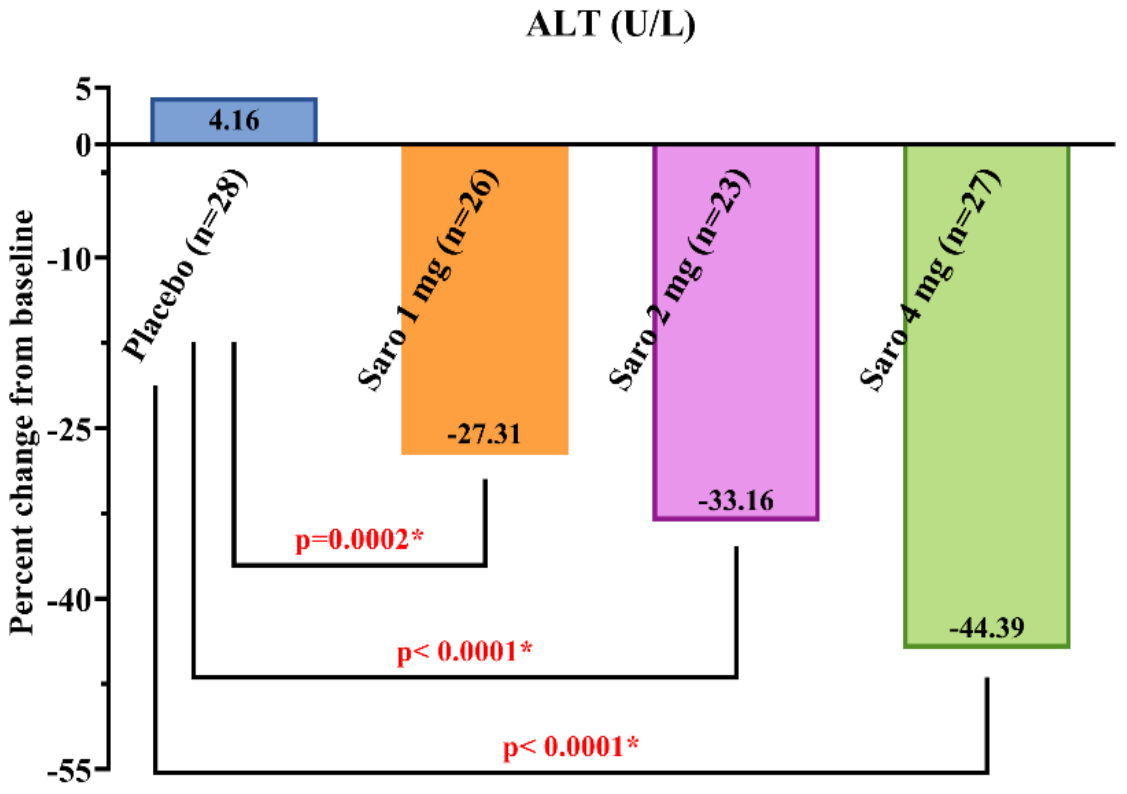
Amin et al; AASLD 2019



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

EVIDENCES IV: Saroglitazar PPAR α/γ agonist in Patients with NASH (16-weeks)



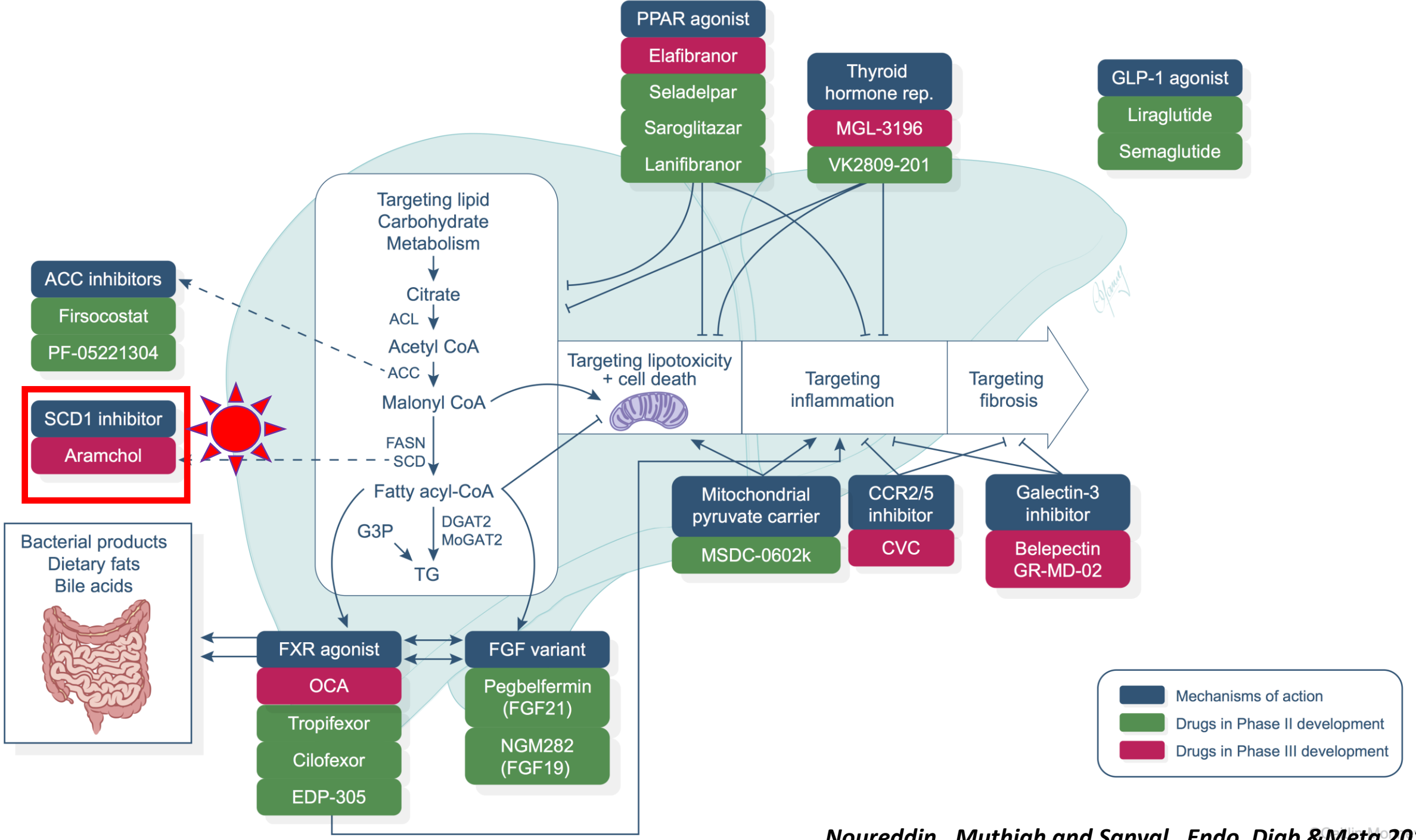


Gawrieh S et al; AASLD 2019 LO10

A Randomized, Double-blind, Placebo-controlled, Multicenter, Dose-range, Proof-of-concept, 24-week Treatment Study of IVA337 (Lanifibranor) (Pan-PPAR) in NASH

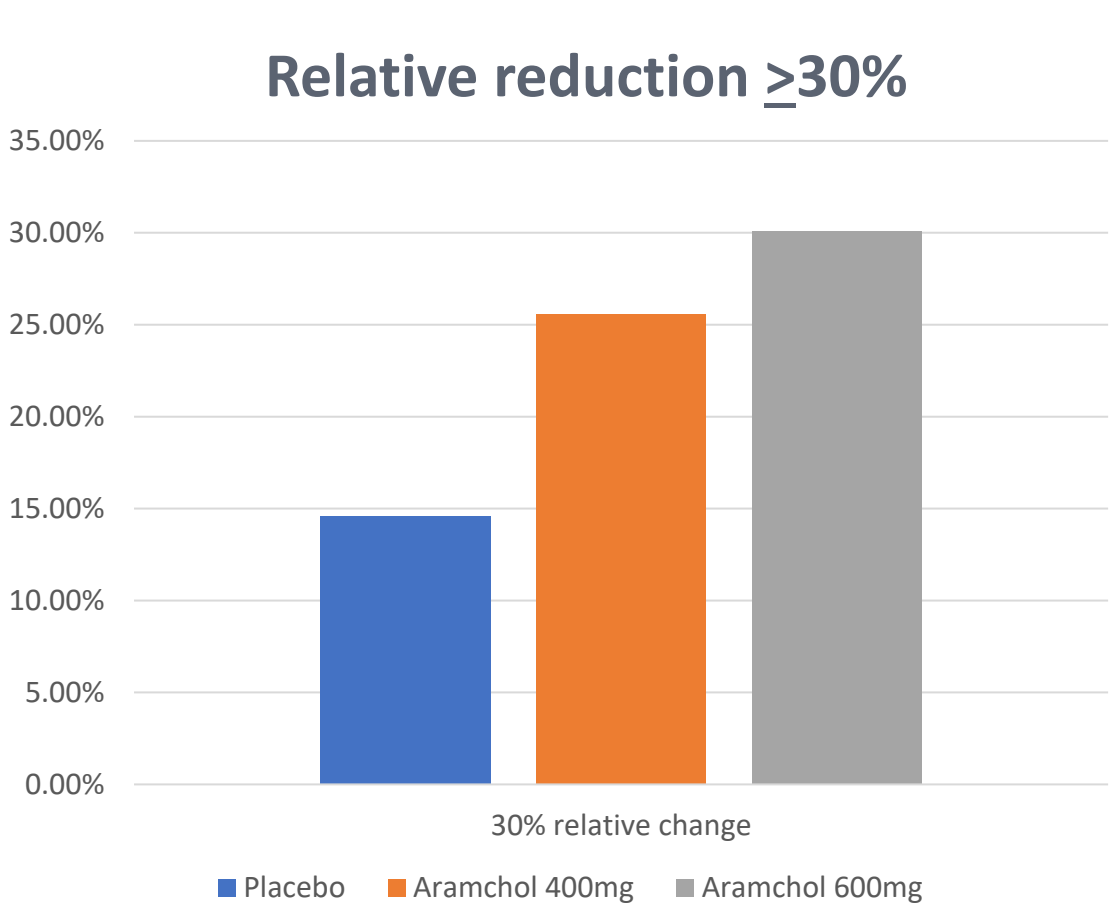
		Intention to Treat Population (ITT)			Per Protocol Population (PP)		
		Placebo (N = 81)	Lanifibranor		Placebo (N = 62)	Lanifibranor	
			800mg (N = 83)	1200mg (N = 83)		800mg (N = 63)	1200mg (N = 69)
Primary endpoint	≥ 2 points of SAF activity score[1]	27%	41% *P=0.061*	49% *P=0.004**	34%	51% *P=0.058*	55% *P=0.015**
Secondary endpoints	Resolution of NASH and no worsening of fibrosis[2]	19%	33% *P=0.043**	45% *P<0.001**	23%	40% *P=0.039**	49% *P=0.002**
	Resolution of NASH and no worsening of fibrosis[2] in F2/F3 patients[3]	9%	34% *P=0.011**	44% *P<0.001**	11%	40% *P=0.016**	51% *P<0.001**
	Improvement of fibrosis by at least one stage and no worsening of NASH [4]	24%	28% *P=0.53*	42% *P=0.011**	29%	32% *P=0.75*	46% *P=0.04**
	Resolution of NASH and improvement of fibrosis [5]	7%	21% *P=0.017**	31% *P<0.001**	10%	24% *P=0.036**	33% *P=0.001**
	Decrease of ≥ 2 points of NAS score [6] (NAFLD activity score) and no worsening of fibrosis	32%	52% *P=0.01**	64% *P<0.001**	40%	62% *P=0.02**	71% *P<0.001**

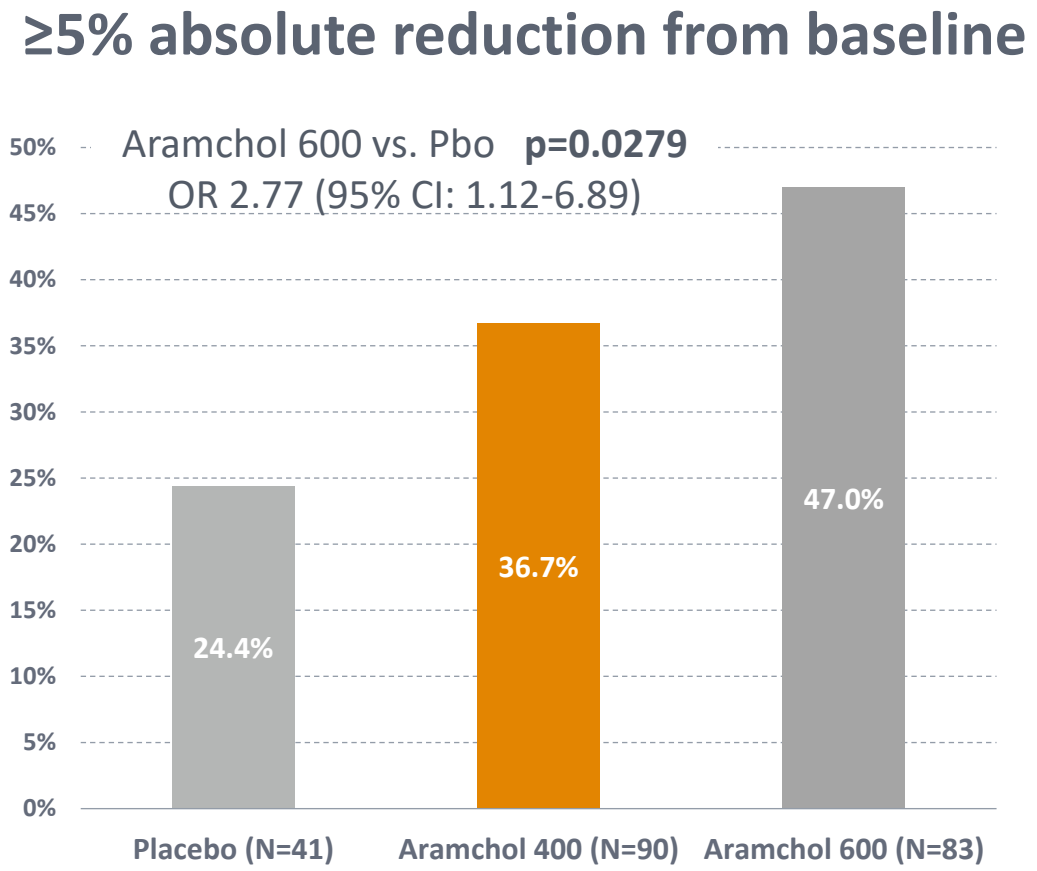
Source press release: https://inventivapharma.com/wp-content/uploads/2020/06/Inventiva-PR-NATIVE-top-line-results-EN-15062020.pdf



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

ARREST: A one year global phase 2b randomized placebo-controlled trial



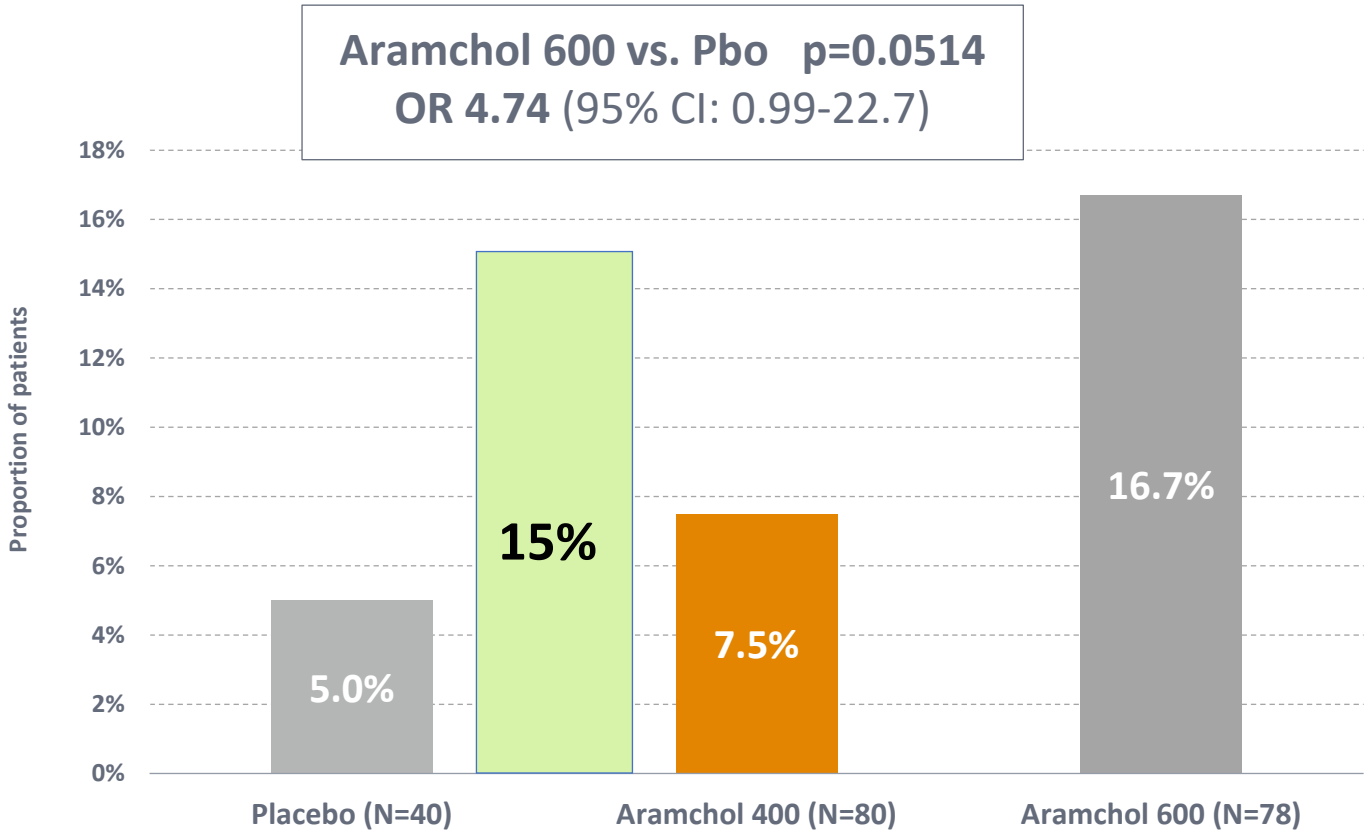


Absolute change from baseline vs. placebo: 400mg **-3.32%,** p=0.0450; 600mg **-3.09%** p=0.0655

Ratziu et el; EASL 2019

Aramchol: NASH Resolution without worsening of Fibrosis

Mean stage: 2.00±0.96
F2/3: 60%
NAS ≥ 5: 70%



Average placebo response
FLINT, PIVENS, GENFIT, LEAN

- In subgroups of F2/3, NAS>4; Abnormal AST/AST, BMI≥30; HbA1C≥6.4%: NASH resolution was noted in a larger proportion of patients in the 600mg group vs. placebo

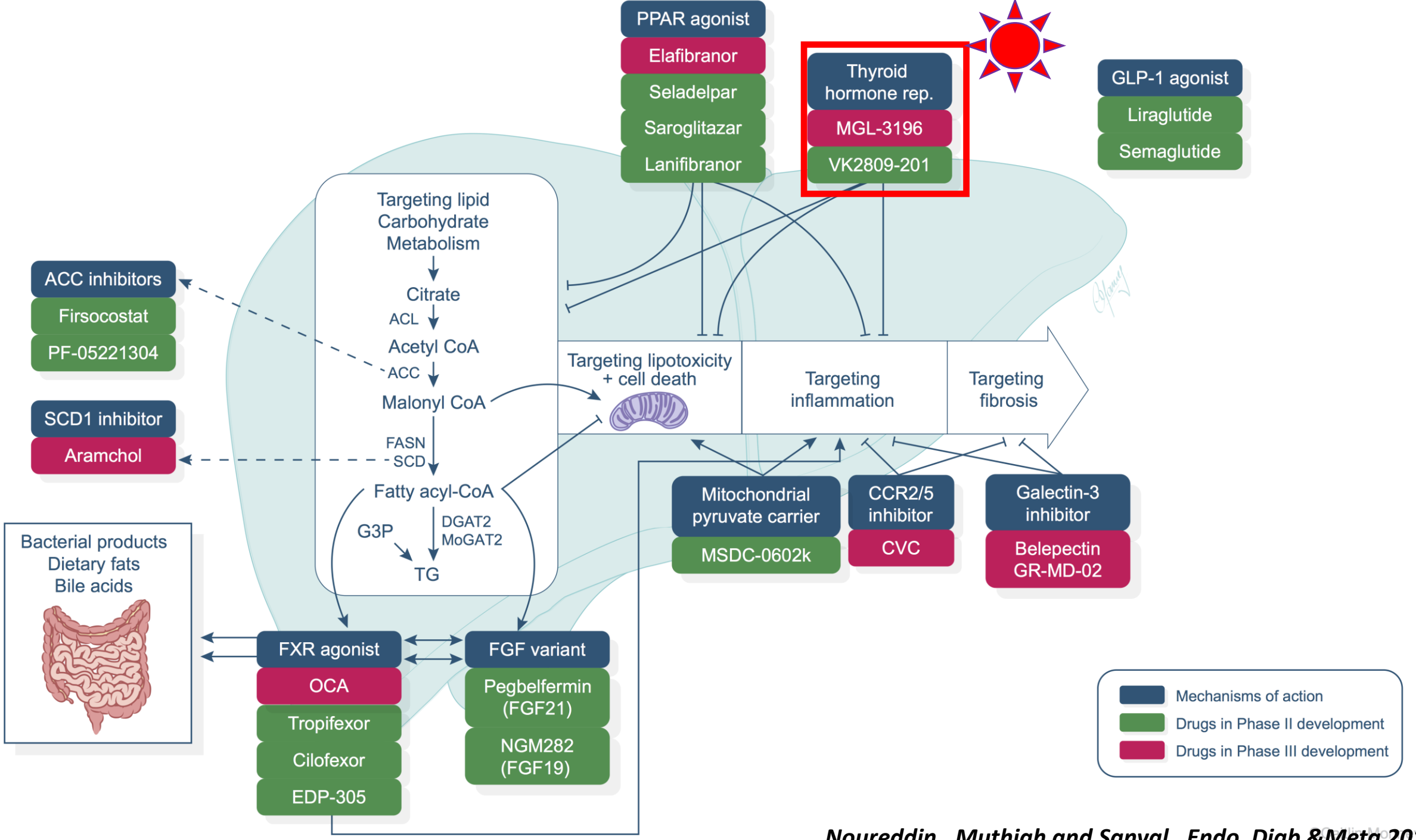
Ratziu et el; EASL 2019

Others in the DNL pathway: FASCINATE-1, the Phase 2 clinical trial of its oral, once-daily FASN inhibitor TVB-2640

	TVB-2640 50 mg (n=28)	TVB-2640 25 mg (n=30)	Placebo (n=27)
Mean relative change in liver fat	-28.2%	-9.6%	+4.5%
P-value vs placebo	*p=0.0011*	*p=0.0535*	
Patients achieving ≥30% reduction in liver fat (responder rate)	60.7%	23.3%	11.1%
P-value vs placebo	*p=0.0008*	*p=0.2281*	

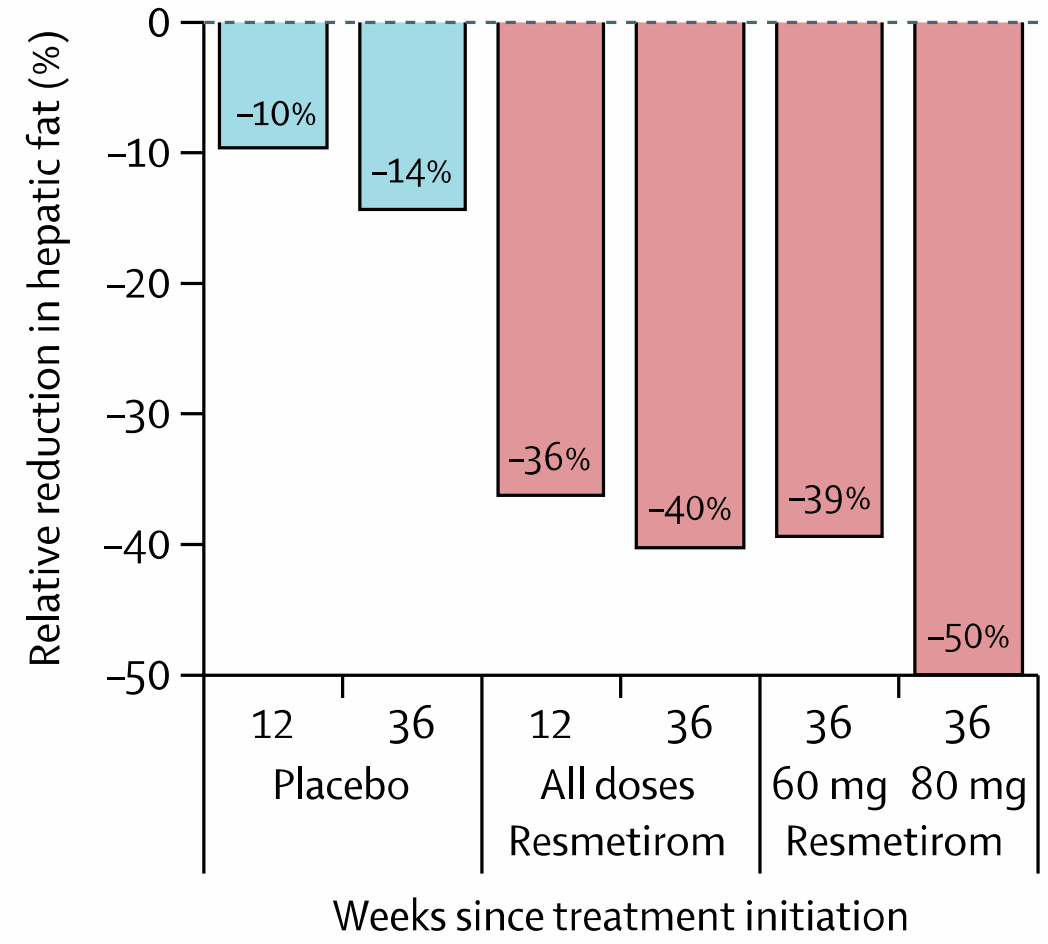
TVB-2640 also significantly decreased ALT by up to 20.4% and LDL-cholesterol by up to 7.6% at week 12

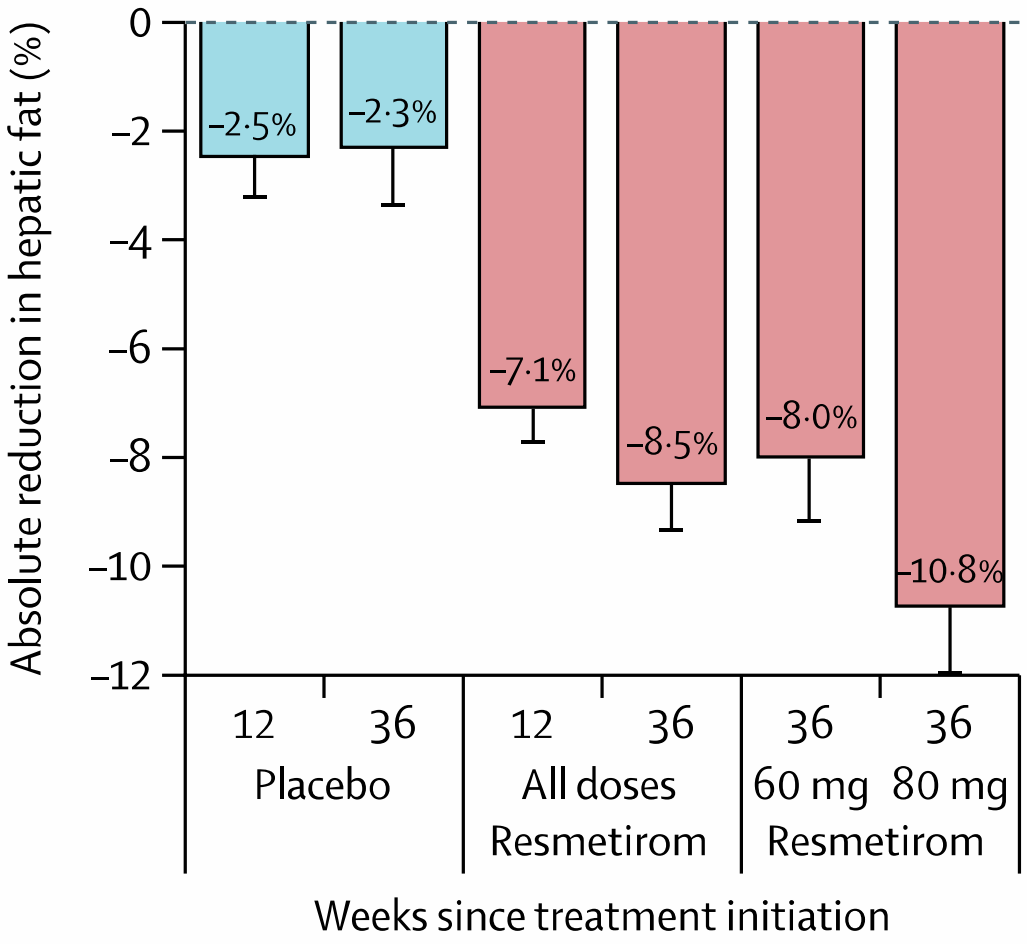
Source : Press Release



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

Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial





Harrison S, et al, The Lancet Dec 2019

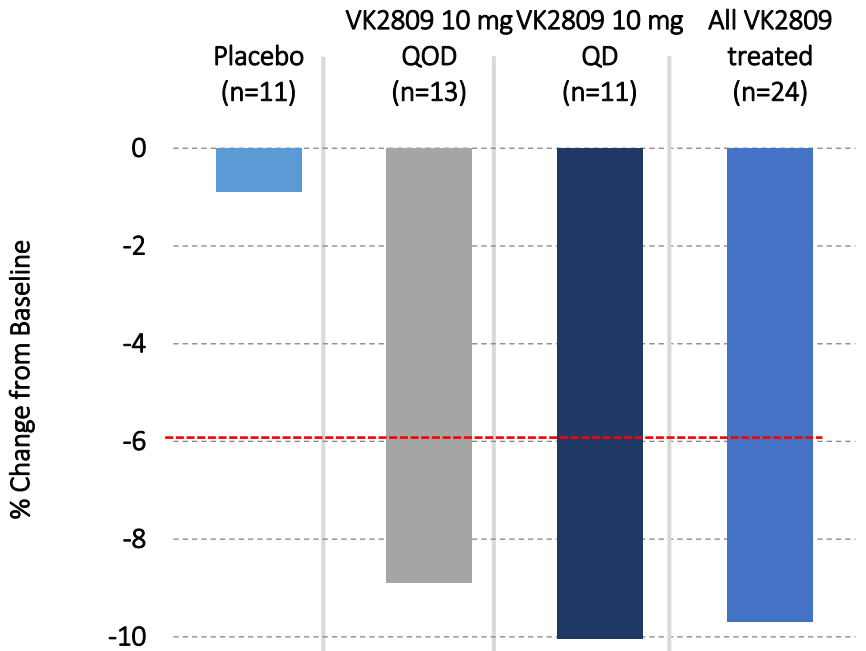
Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

	n	Placebo, n (%)	n	Resmetirom, n (%)	Odds ratio	p value
≥2-point NAS reduction	34	11 (32·4%)	73	41 (56·2%)	2·7 (1·1–6·3)	0·024
High exposure group	..	..	43	28 (65·1%)	3·9 (1·5–10·1)	0·0059
Low exposure group	..	..	30	13 (43·3%)	1·6 (0·6–4·4)	0·44
High SHBG group	..	..	44	28 (63·6%)	3·7 (1·4–9·4)	0·012
Low SHBG group	..	..	29	13 (44·8%)	1·7 (0·6–4·7)	0·44
MRI-PDFF responder	..	..	46	32 (69·6%)	4·8 (1·8–12·4)	0·0014
<5% weight loss group	27	5 (18·5%)	61	30 (49·2%)	4·3 (1·4–12·7)	0·0090
NASH resolution (without fibrosis worsening)	31	6 (6·5%)	73	18 (24·7%)	4·75 (1·03–21·9)	0·032
MRI-PDFF responder	..	..	46	17 (37·0%)	8·50 (1·80–40·2)	0·0026
Including weight loss >9·5%	34	5 (14·7%)	73	18 (24·7%)	1·9 (0·64–5·6)	0·32
MRI-PDFF responder (including weight loss >9·5%)	..	..	46	17 (37·0%)	3·4 (1·1–10·4)	0·042
Fibrosis responder	34	8 (23·5%)	73	21 (28·8%)	1·3 (0·51–3·36)	0·65
MRI-PDFF responder	..	..	46	15 (32·6%)	1·6 (0·58–4·29)	0·46
NASH resolution responder	..	..	18	11 (61·1%)	5·1(1·5–17·6)	0·014

Harrison S, et al, The Lancet Dec 2019

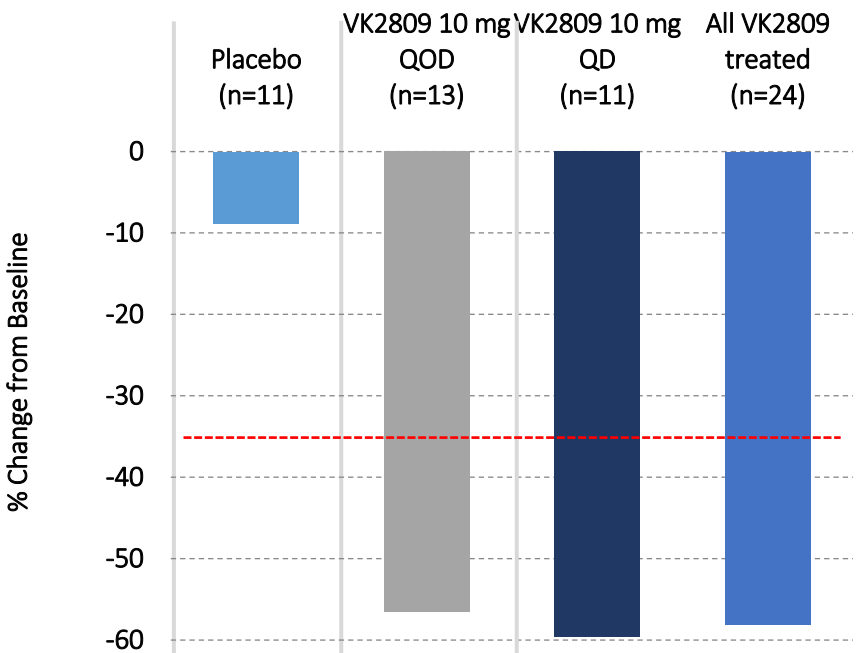
VK2809-201: Change in Liver Fat

Mean Absolute % Change in Liver Fat at 12 Weeks



	Placebo (n=11)	VK2809 10 mg QOD (n=13)	VK2809 10 mg QD (n=11)	All VK2809 treated (n=24)
% Change (SD)	-0.9% (2.8)	-8.9% (6.2)	-10.6% (5.2)	-9.7% (5.7)
p-value vs. placebo	-	0.011	0.0025	0.0019

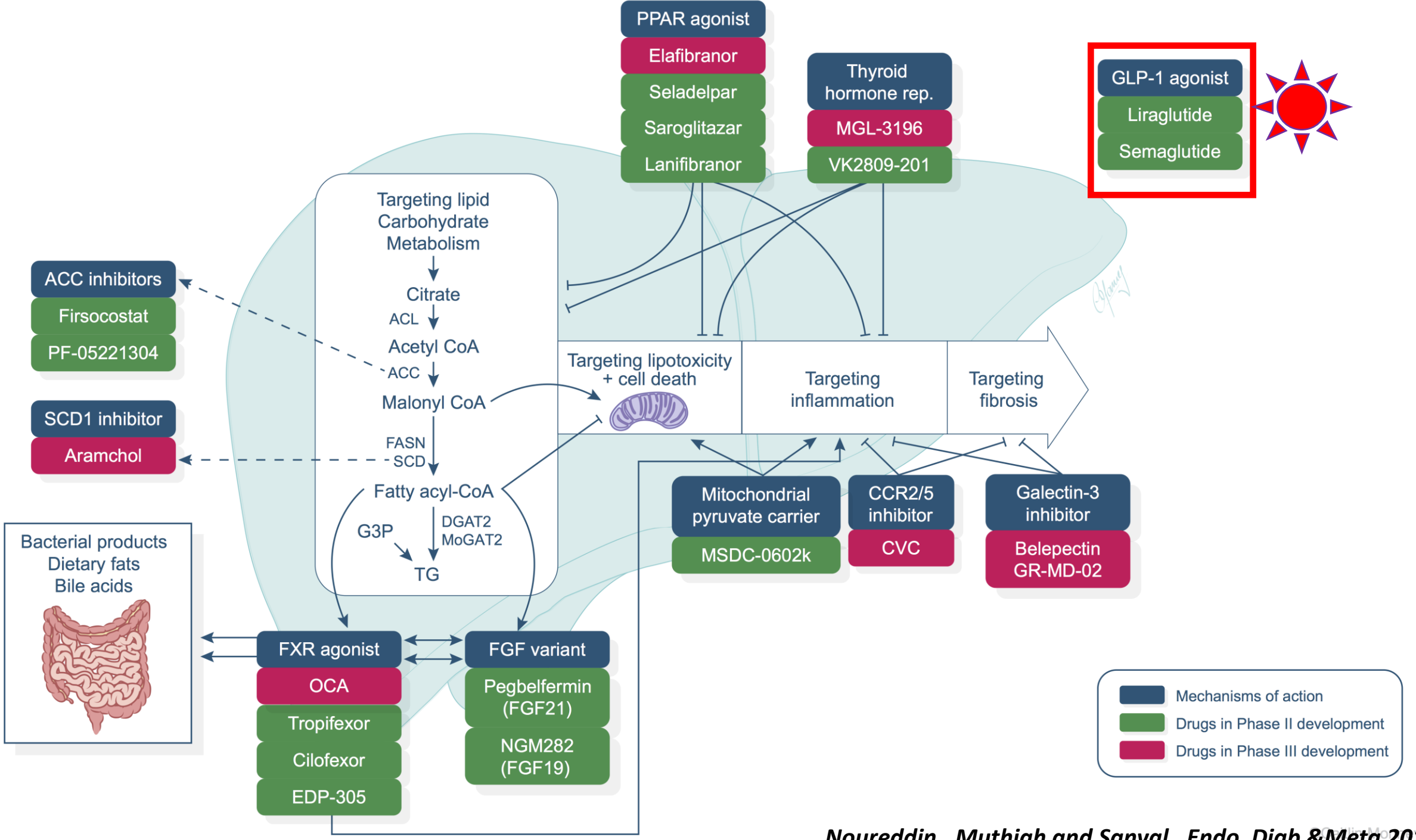
Median Relative % Change in Liver Fat at 12 Weeks



	Placebo (n=11)	VK2809 10 mg QOD (n=13)	VK2809 10 mg QD (n=11)	All VK2809 treated (n=24)
% Change	-8.9%	-56.5%	-59.7%	-58.1%
p-value vs. placebo	-	0.0014	0.0003	0.0002

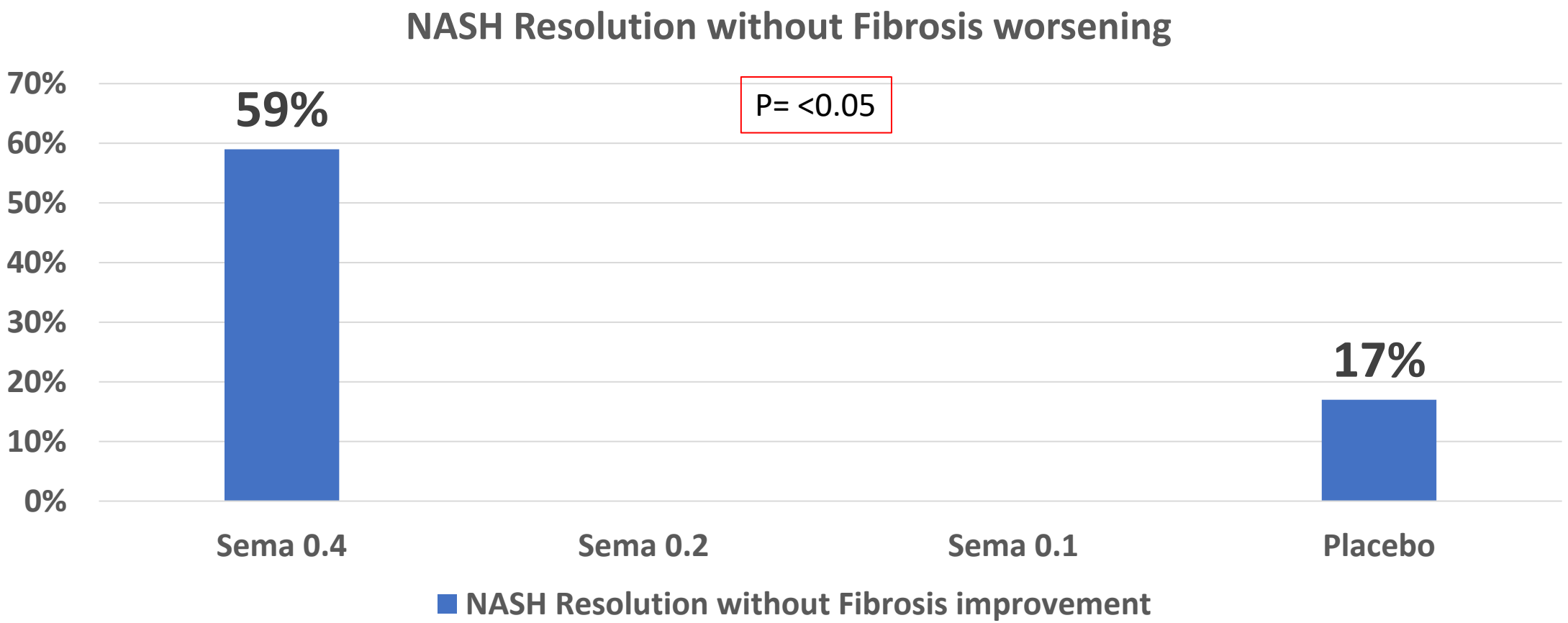
Patients receiving VK2809 experienced relative reductions of up to 72% (10 mg QOD) to 76% (10 mg QD) at Week 12

Loomba et al; 2019

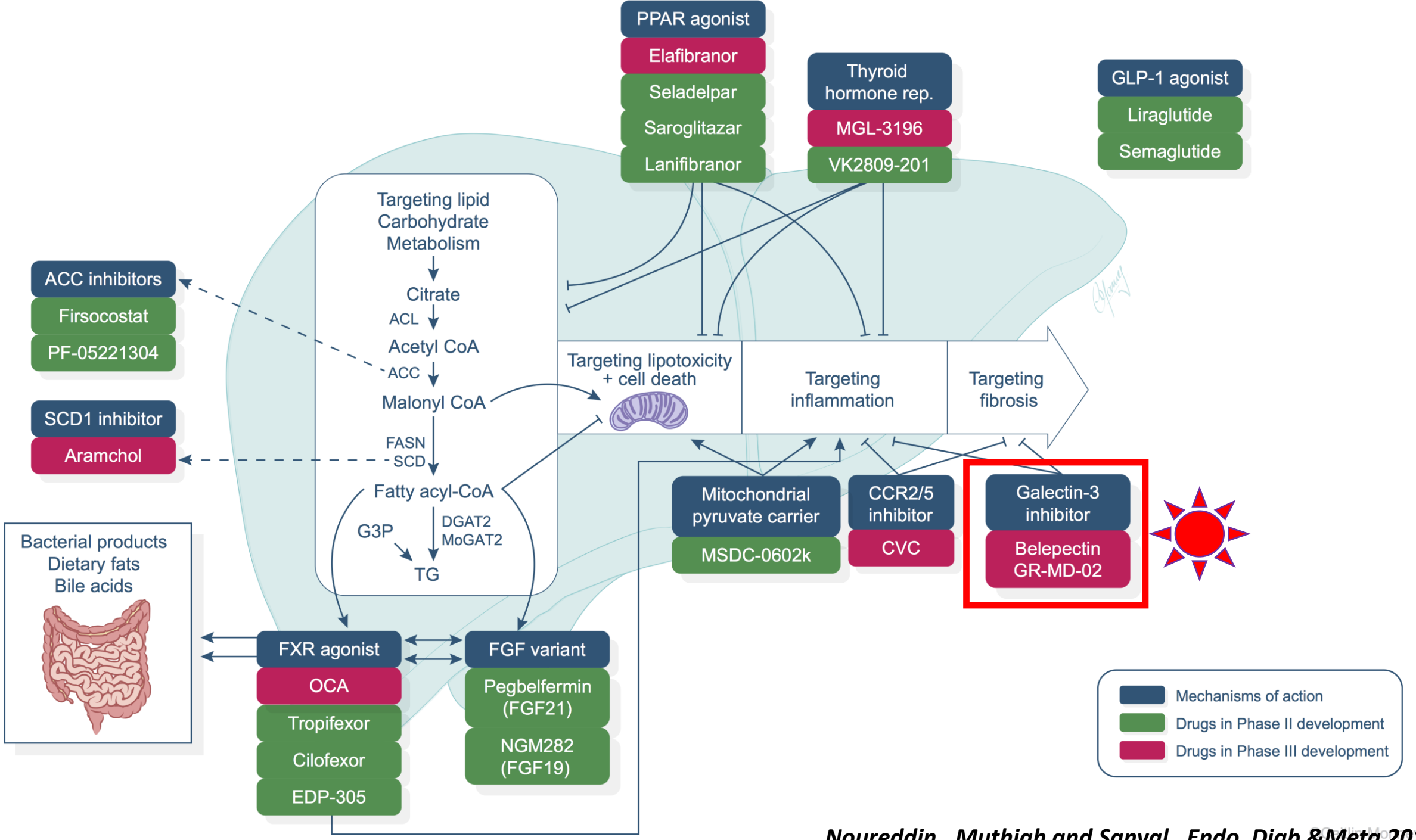


Noureddin , Muthiah and Sanyal . Endo, Diab &Meta 2019

Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects With Non-alcoholic Steatohepatitis (72 weeks).

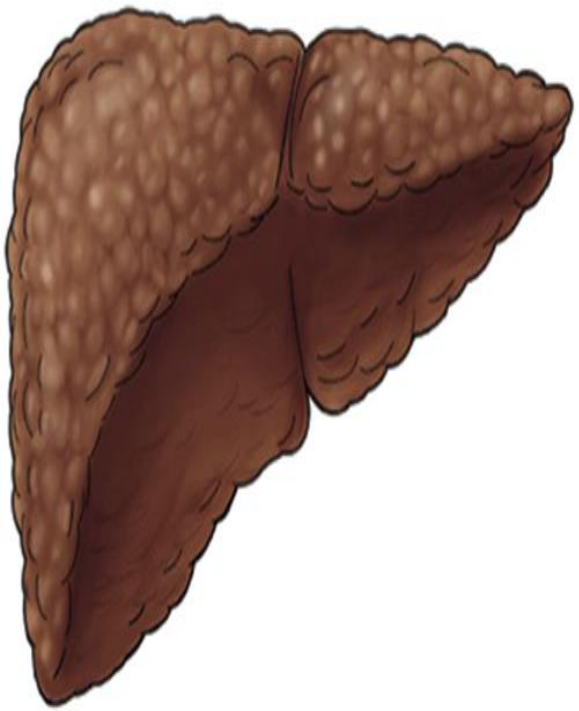


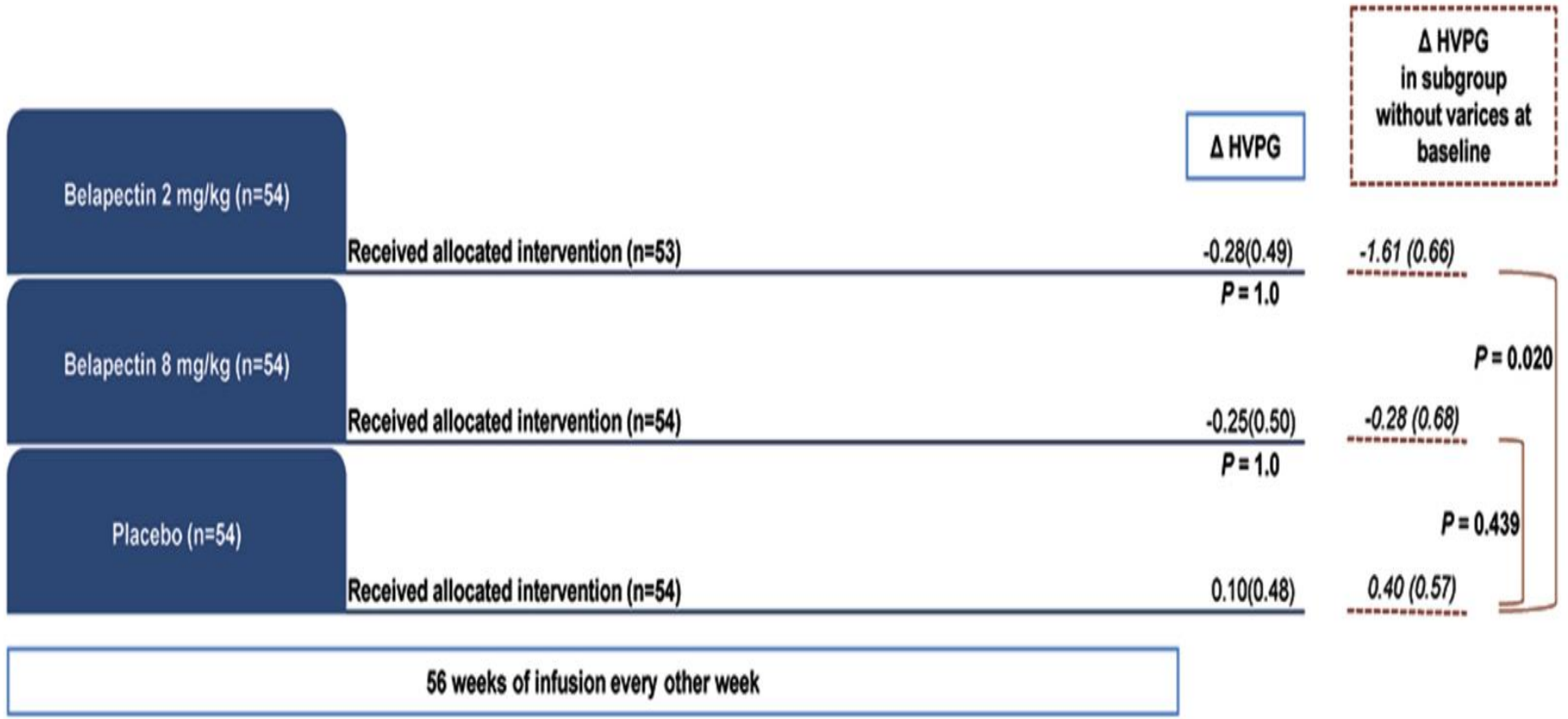
Source Press Release 2020



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

Effects of Belapectin, an Inhibitor of Galectin-3, in Patients With NASH With Cirrhosis and Portal Hypertension



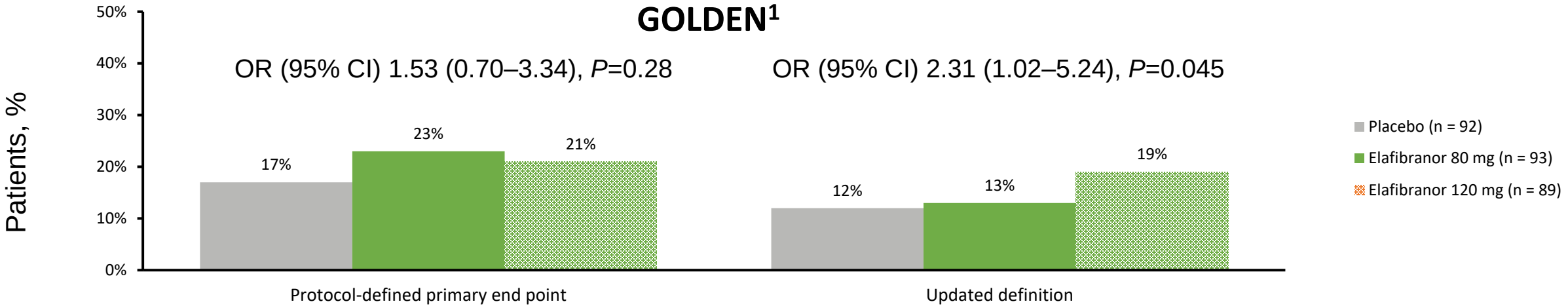


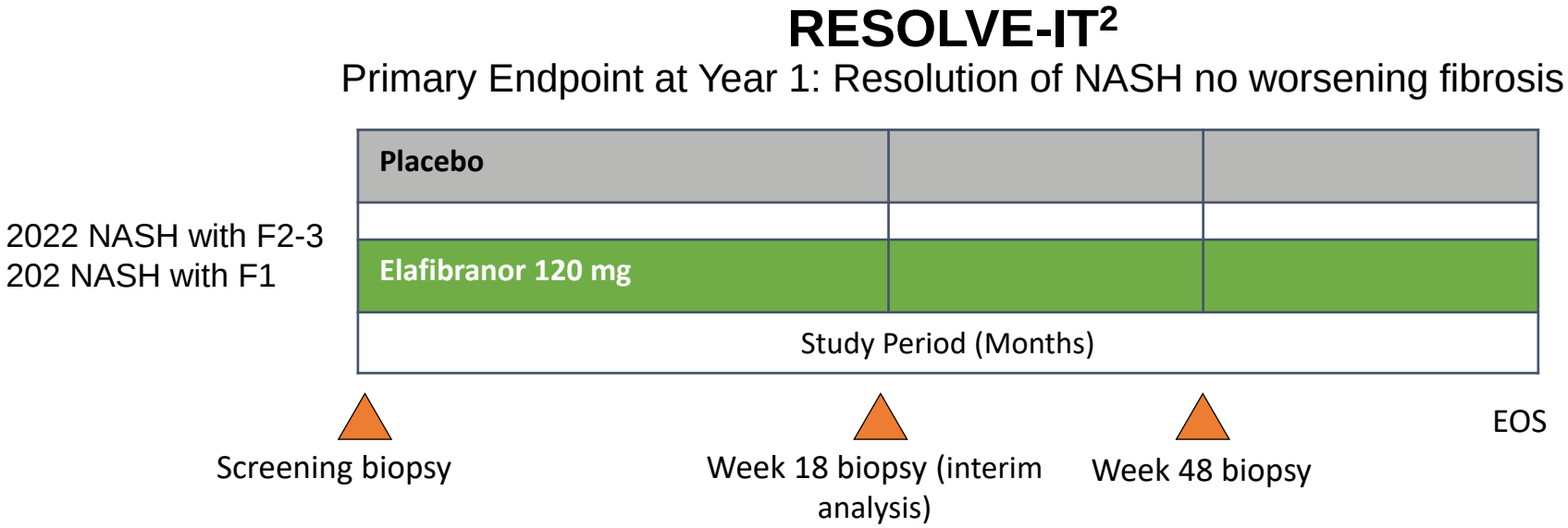
Chalasani et al: Gastroenterology 2020

Didn’t Make it to the Finish Line!
But Many Lessons Learned!!

Elafibranor: GOLDEN and RESOLVE-IT

505-Peroxisome Proliferator-Activated Receptors (PPAR α/δ Pathways)





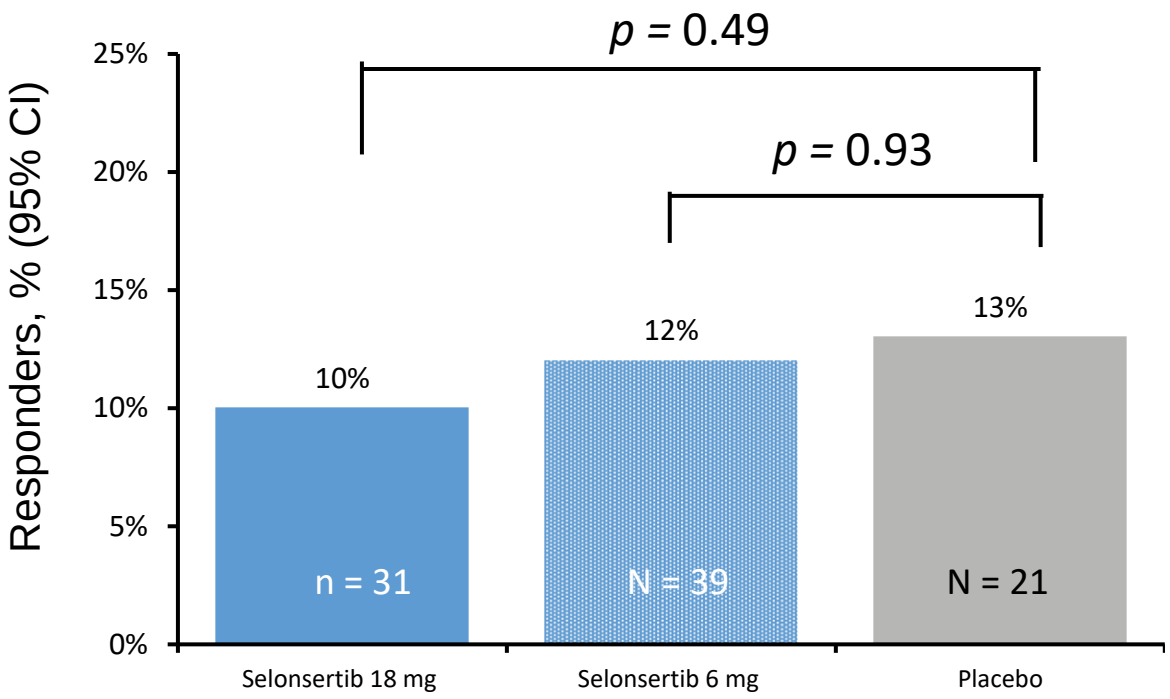
Ratziu V, et al. Gastroenterology. 2016

(RESOLVE-IT). ClinicalTrials.gov Identifier: NCT02704403. 2016.

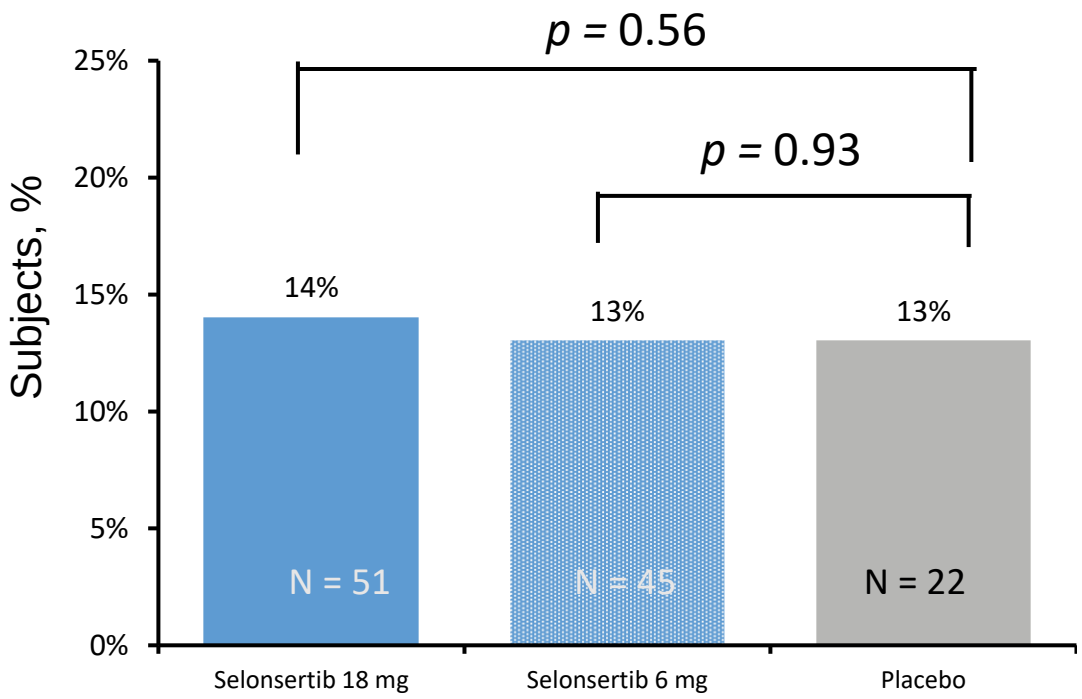
Selonsertib: STELLAR-3 and STELLAR-4

Fibrosis Improvement Without Worsening of NASH

STELLAR-3

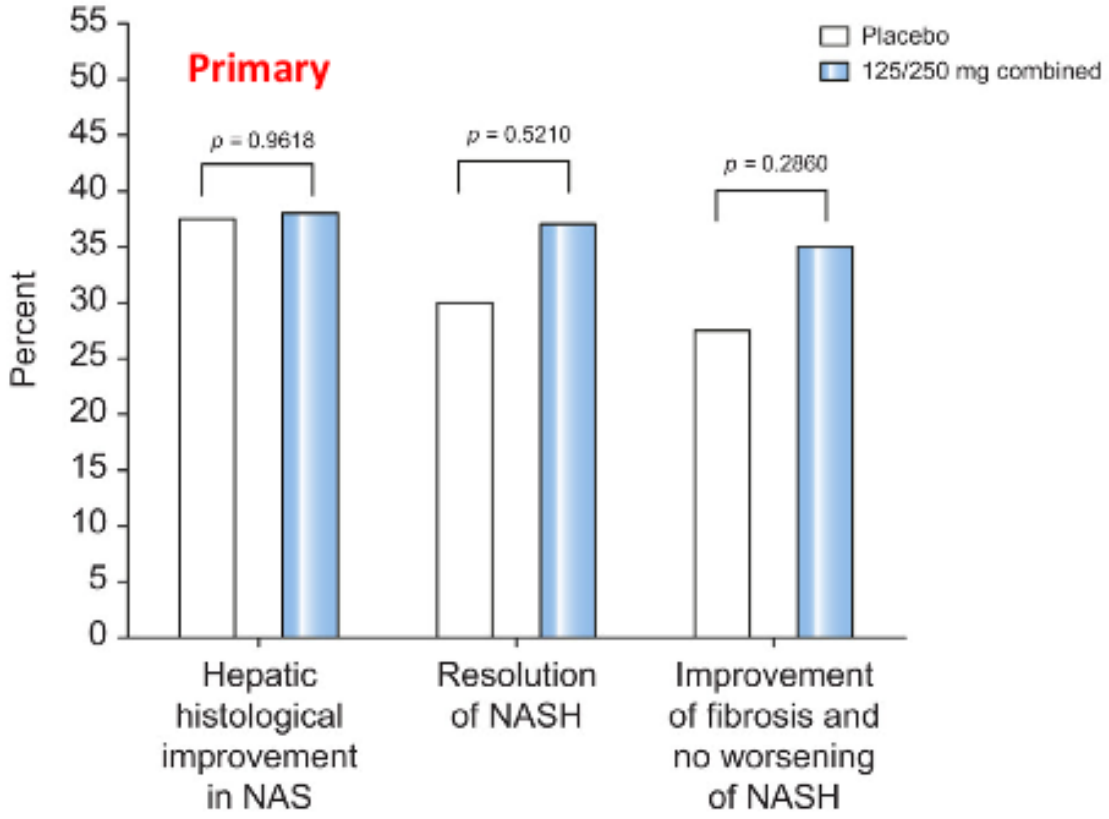


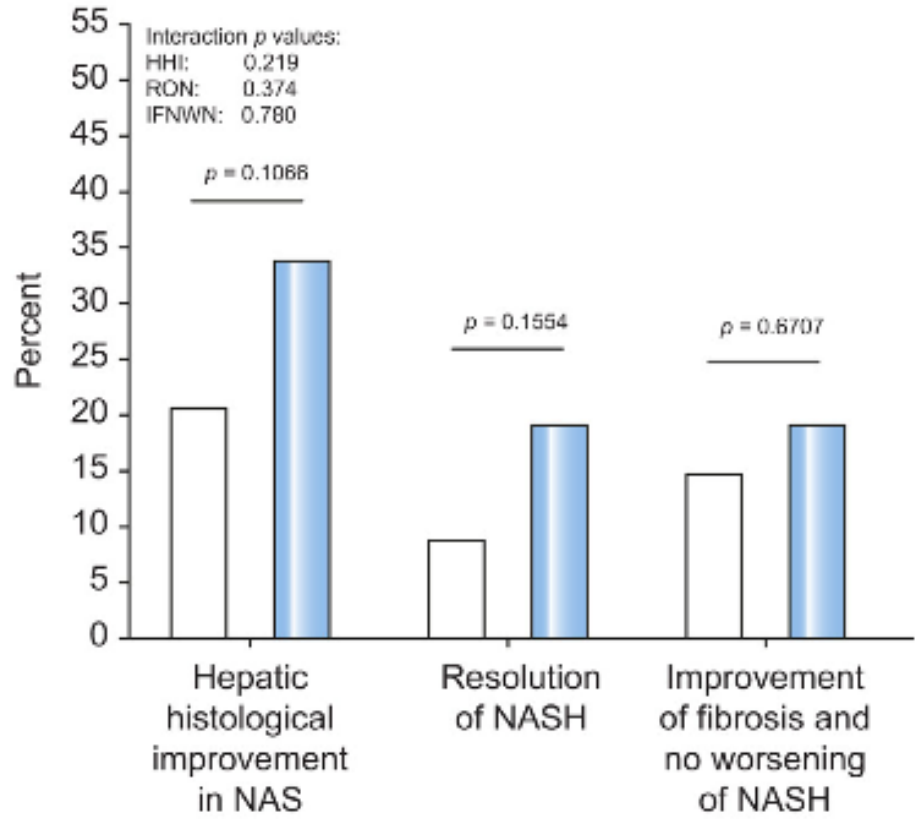
STELLAR-4



Harrison SA, et al J Hep 2020

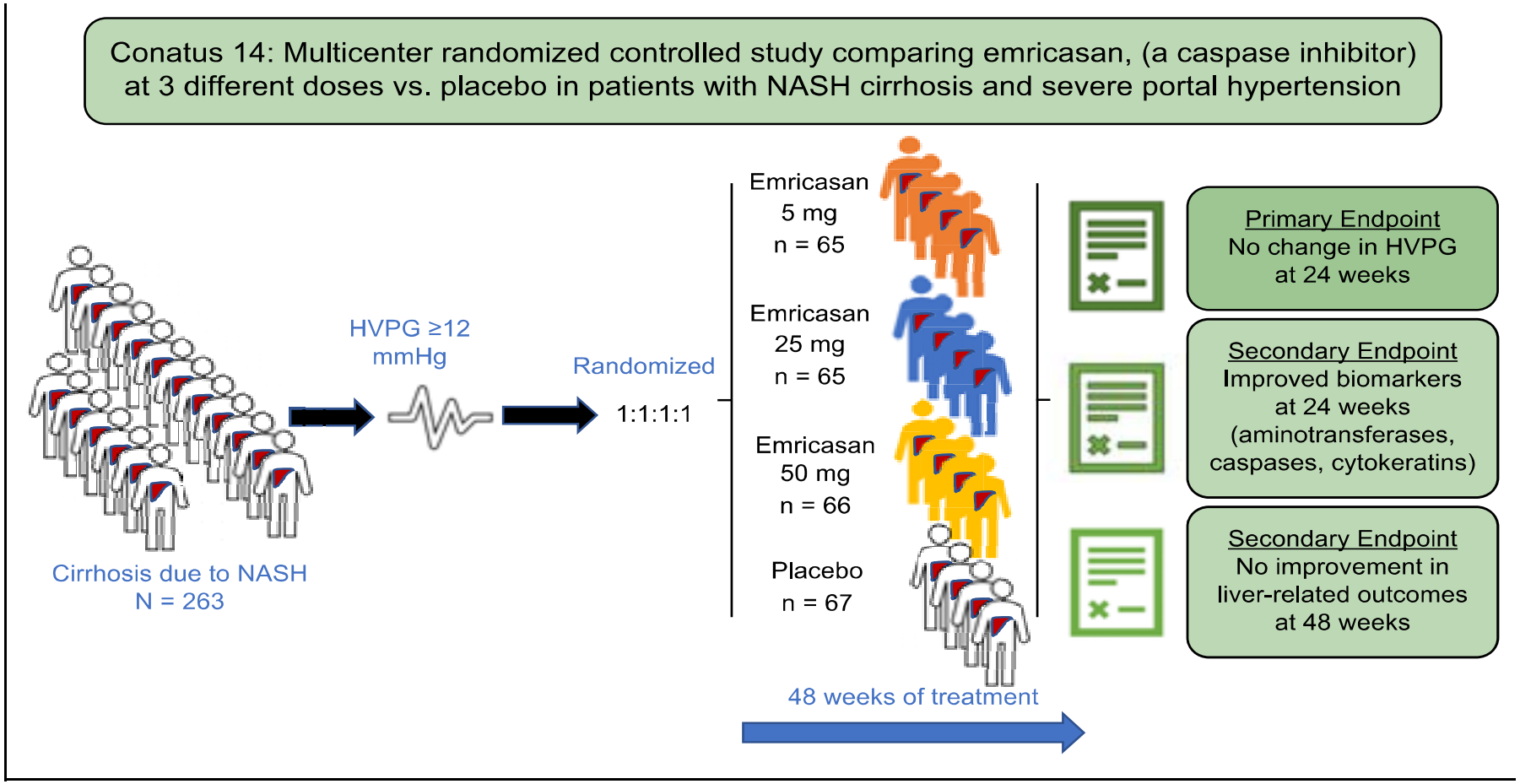
Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase IIb study (52-weeks)





Harrison et al; J Hep 2020

Conatus All Three Trials in Cirrhotics



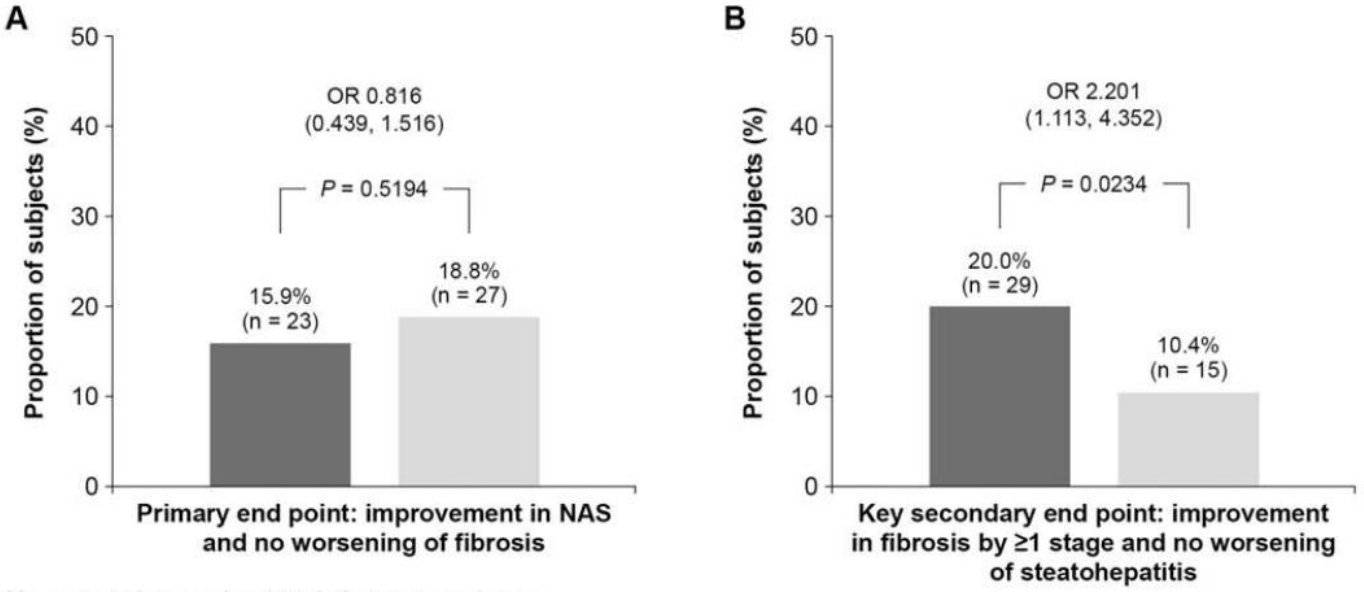
Garcia-Tsao et al; J Hep 2020

What are still waiting for in 2020?

Cenicriviroc in Pre-Cirrhotic NASH (Allergan)

CENTAUR phase 2 trial was basis for phase 3

- Analysis after 1 year of therapy



- Analysis of the data after 2 years of treatment was not as strong'The difference between placebo and treated was not different on the endpoint of a one stage reduction in fibrosis at 2 years

CCR2/CCR5 inhibitor

AURORA Phase 3 Trial

- NASH with fibrosis stage 2-3
- N=2000
- Placebo vs. cenicriviroc 150 mg daily
- Interim subpart H endpoint: Fibrosis reduction at 12 months
- Clinical outcome composite ~5 years
- Anticipated interim October 2021

Friedman, et al. Hepatology 2018;67:1754-1767

Slide Courtesy of Prof. Naga Chalasani

Phase 2 trials with combination therapy for non-cirrhotic NASH/NAFLD.

Combination	NCT number	Study design	Patient groups	Treatment & duration	Primary outcomes
PF-05221304 (liver specific ACC inhibitor) and PF-06865571 (DGAT2 inhibitor	NCT03776175 (Pfizer) **6 week s**) **tudy**	Randomized, double-blind, placebo-controlled parallel group	98 NAFLD patients	Monotherapy of each drug (15 mg PF-05221304 vs. placebo twice daily for 41 days or 300 mg of PF-06865571 twice daily for 41 days) Combined therapy: 15 mg PF-05221304 and 300 mg PF-06865571 twice daily for 41 days	**Relative change in liver fat as assessed by MRI-PDFF at day 42**
Tropifexor (LJN452), Cenicriviroc (CVC)	**NCT03517540** - TANDEM (Novartis Pharmaceutical) **48 weeks**	Phase II, randomized double-blind, multicenter	200 NASH patients with fibrosis	1. Tropifexor monotherapy, 2. CVC monotherapy, 3. Tropifexor dose 1 plus CVC and 4. Tropifexor dose 2 plus CVC for 48 weeks	Number of patients with AEs or SEAs
Semaglutide, firsocostat (GS-0976, ACC inhibitor), cilofexor (GS-9674, FXR agonist)	**NCT03987074** (Gilead Sciences, and Novo Nordisk A/S) **6 month study**	Phase II, POC, open-label, randomized study	100 NASH patients	1. Semaglutide 0.24 mg – 2.4 mg (dose escalation every 4 weeks) for 24 weeks, 2. Semaglutide 0.24 mg – 2.4 mg (dose escalation every 4 weeks) plus firsocostat 20 mg for 24 weeks, 3. Semaglutide 0.24 mg – 2.4 mg (dose escalation every 4 weeks) plus cilofexor 30 mg for 24 weeks, 4. Semaglutide 0.24 mg – 2.4 mg (dose escalation every 4 weeks) plus cilofexor 100 mg for 24 weeks or 5. Semaglutide 0.24 mg – 2.4 mg (dose escalation every 4 weeks) plus firsocostat 20 mg and cilofexor 30 mg for 24 weeks	**Number of patients who experience TEAEs, SAEs, and any grade ≥ 1 laboratory abnormality Efficacy endpoints at 24 weeks**

Slide Courtesy of Prof. Naga Chalasani

Phase 2 ATLAS Study in Patients With Bridging Fibrosis (F3) and Compensated Cirrhosis (F4) Due to NASH

Week 48 Primary Endpoint - Histologic Responses*

Endpoint, n (%)	FIR (n=33)	CILO (n=34)	SEL/FIR (n=71)	SEL/CILO (n=68)	FIR/CILO (n=67)	Placebo (n=38)
Fibrosis improvement without NASH worsening	4 (12.1%) p=0.94	4 (11.8%) p=0.96	11 (15.5%) p=0.62	13 (19.1%) p=0.26	14 (20.9%) p=0.17	4 (10.5%)

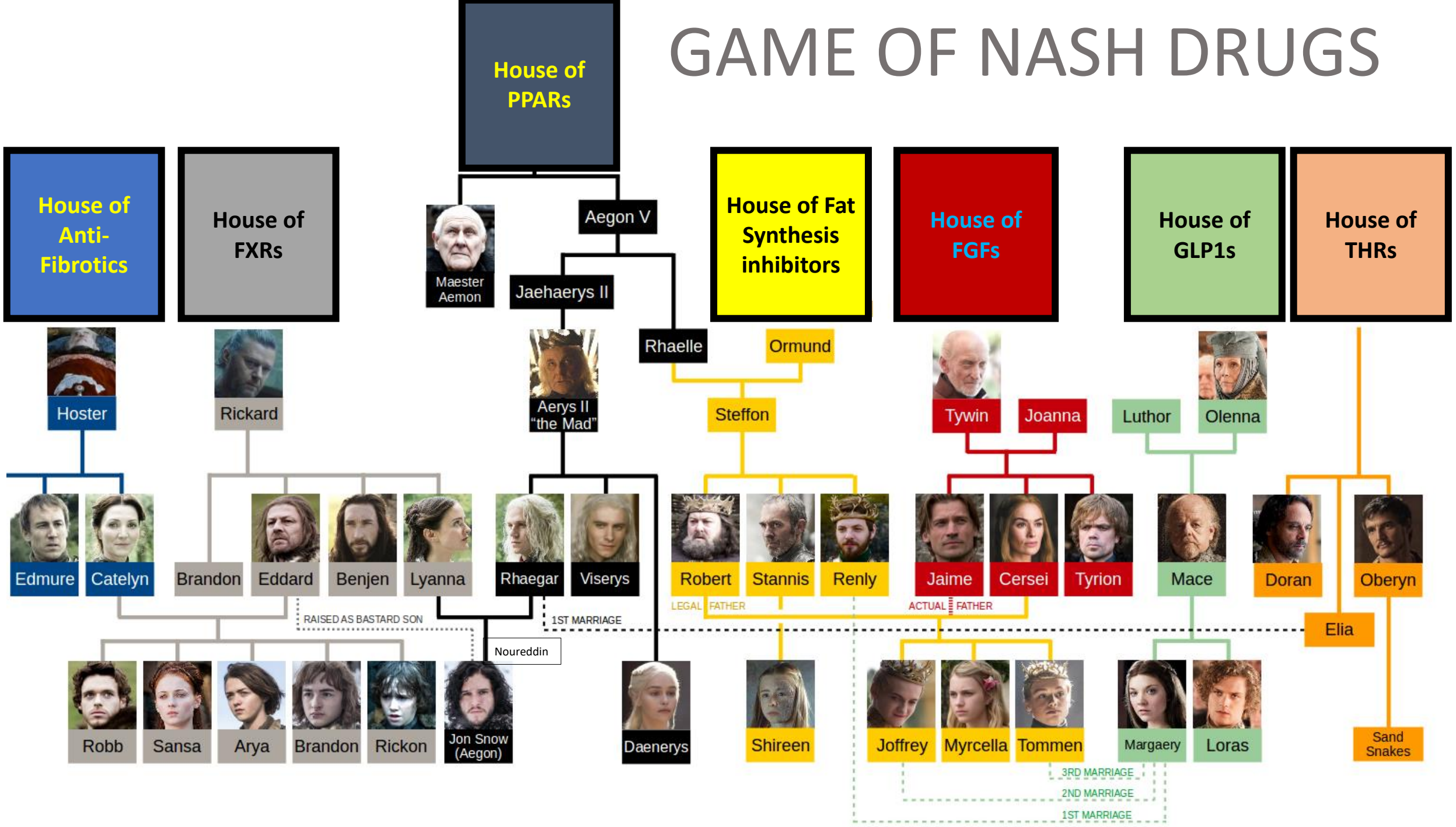
CILO, cilofexor (FXR agonist); FIR, firsocostat (ACC inhibitor); SEL,

Source: Press Release:

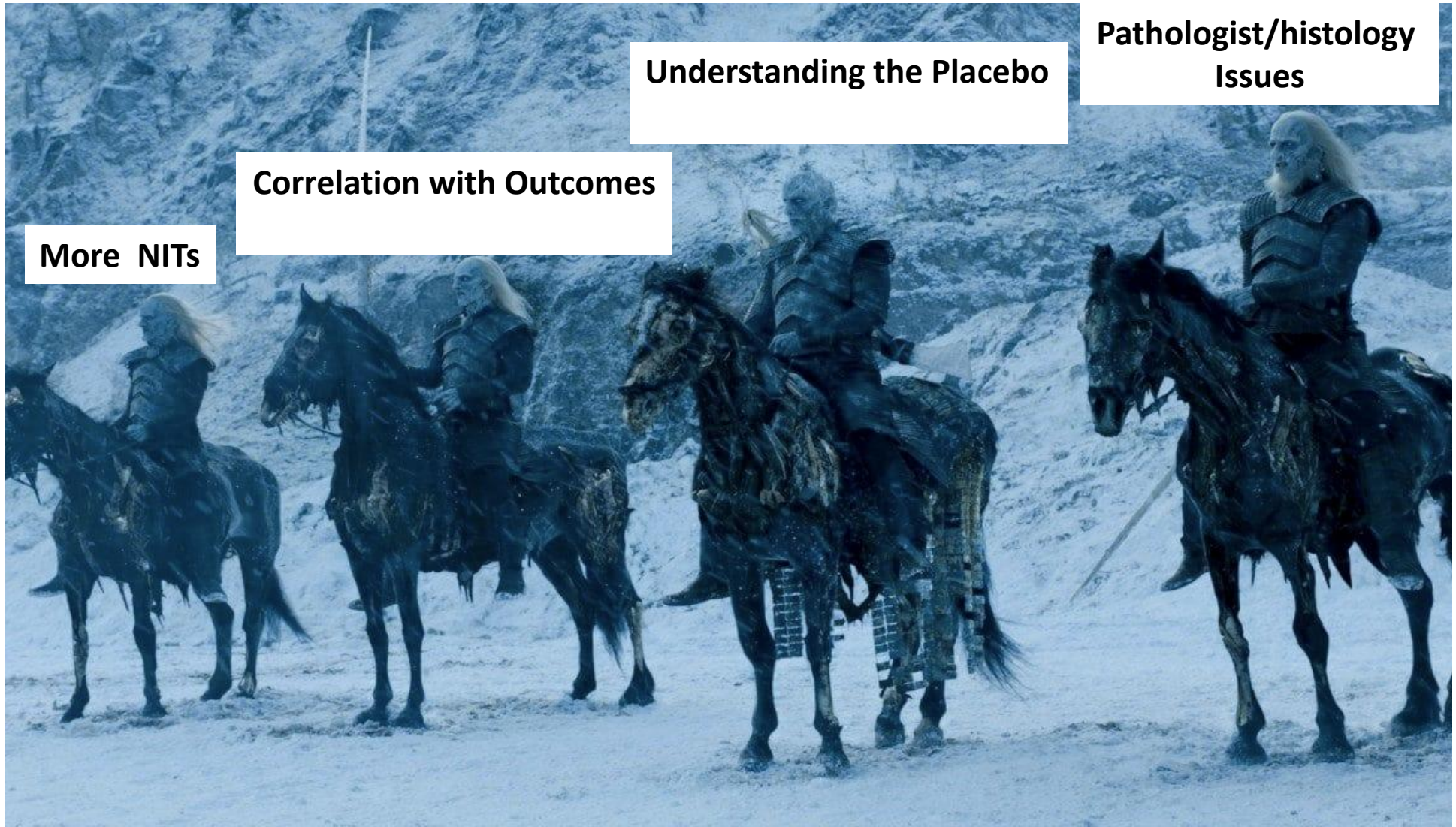
Phase 2 ATLAS Study in Patients With Bridging Fibrosis (F3) and Compensated Cirrhosis (F4) Due to NASH

- Statistically significant improvements in multiple secondary endpoints:
  - ≥2-point reduction in the NAFLD Activity Score (NAS)
  - ≥1-point reductions in steatosis, hepatocellular ballooning and lobular inflammation.
  - Noninvasive tests of fibrosis, liver injury and function, including ALT, AST, bilirubin and ELF score

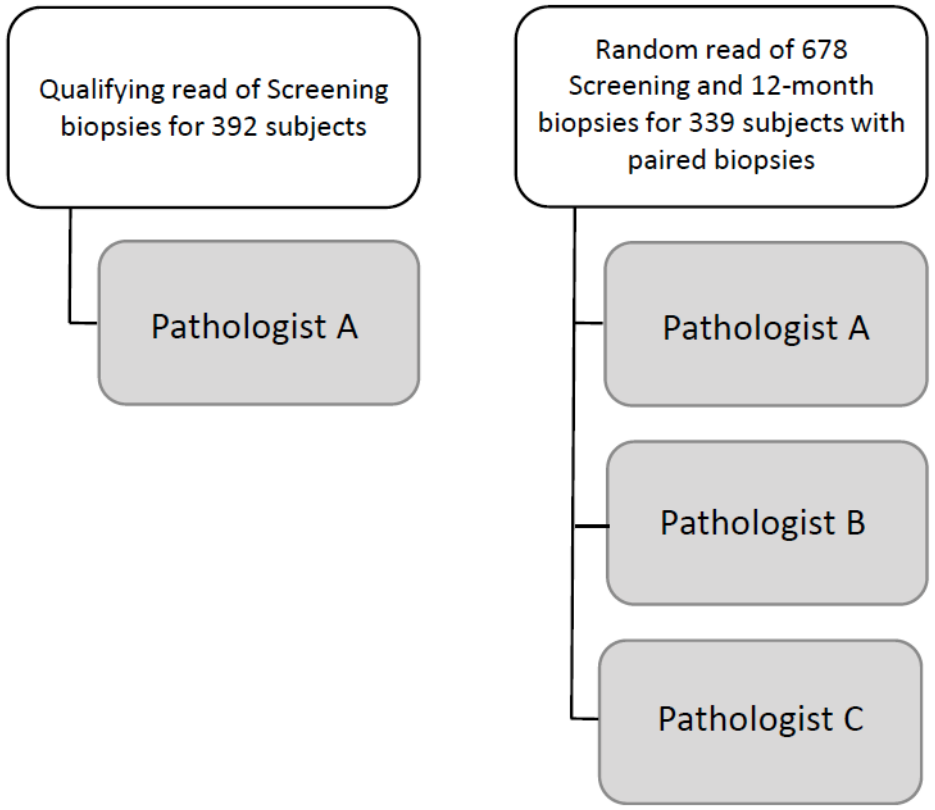
GAME OF NASH DRUGS



We are all in this Together!



Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials



Pathologist B

Pathologist A	No	Yes	N/E
No	64	9	2
Yes	8	16	1
N/E	0	0	0

Unweighted Kappa = 0.490

Pathologist C

Pathologist A	No	Yes	N/E
No	73	2	1
Yes	16	9	0
N/E	0	0	0

Unweighted Kappa = 0.382

Pathologist C

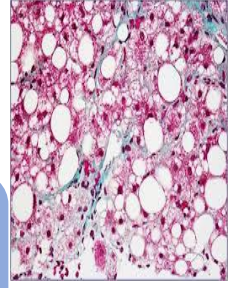
Pathologist B	No	Yes	N/E
No	69	3	0
Yes	18	7	0
N/E	2	1	1

Unweighted Kappa = 0.325

Davidson B et al. J Hep 2020

Placebo Associated Factors in NASH

Hawthorne Effect



Higher baseline NAS

Trials in South America

Frequent Visits

Placebo Effect in NASH

Change in BMI

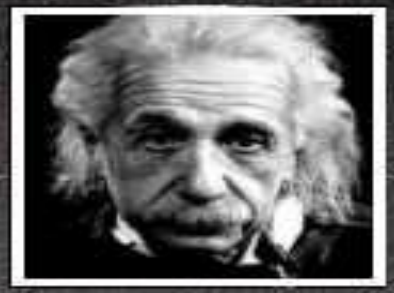
Noureddin, Alkhouri, Noreddin, Curr Hep Reports In press

Implications as of 2020

- More drugs are meeting Phase 2 and phase 3 endpoints
- Lessons learned form the failures
- Histology is and old friend, yet many issues that need to be fixed
- COVID-19 and NASH trials
- Ongoing effort to correlate with hard outcomes
- Multiorgan disease: Efforts to link to other organs especially CV
- Biomarkers:
  - MRI-PDFF
  - Metabolomics
  - Breath test
  - MRE
  - VTCE (FAST)
  - ELF
  - Pro-C3

- Drugs Approval


We all in this together



Don't listen to the person who has the answers; listen to the person who has the questions.

- Albert Einstein

Thank you

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@NoureddinMD