Fondazione IRCCS Policlinico San Matteo

Sistema Socio Sanitario

Regione Lombardia

Pharmacological treatment of NASH

Raffaele Bruno,MD

UNIVERSITÀ DI PAVIA

When a friend dies we feel as if a limb is cut off.

Thomas Jefferson

Agenda

- ✓ **Recommended Pharmacologic Therapies for NASH**

- ✓ **Pipeline Pharmacologic Therapies for NASH**

Agenda

- ✓ **Recommended Pharmacologic Therapies for NASH**

- ✓ Pipeline Pharmacologic Therapies for NASH

Currently Available Drugs for Treatment of NASH

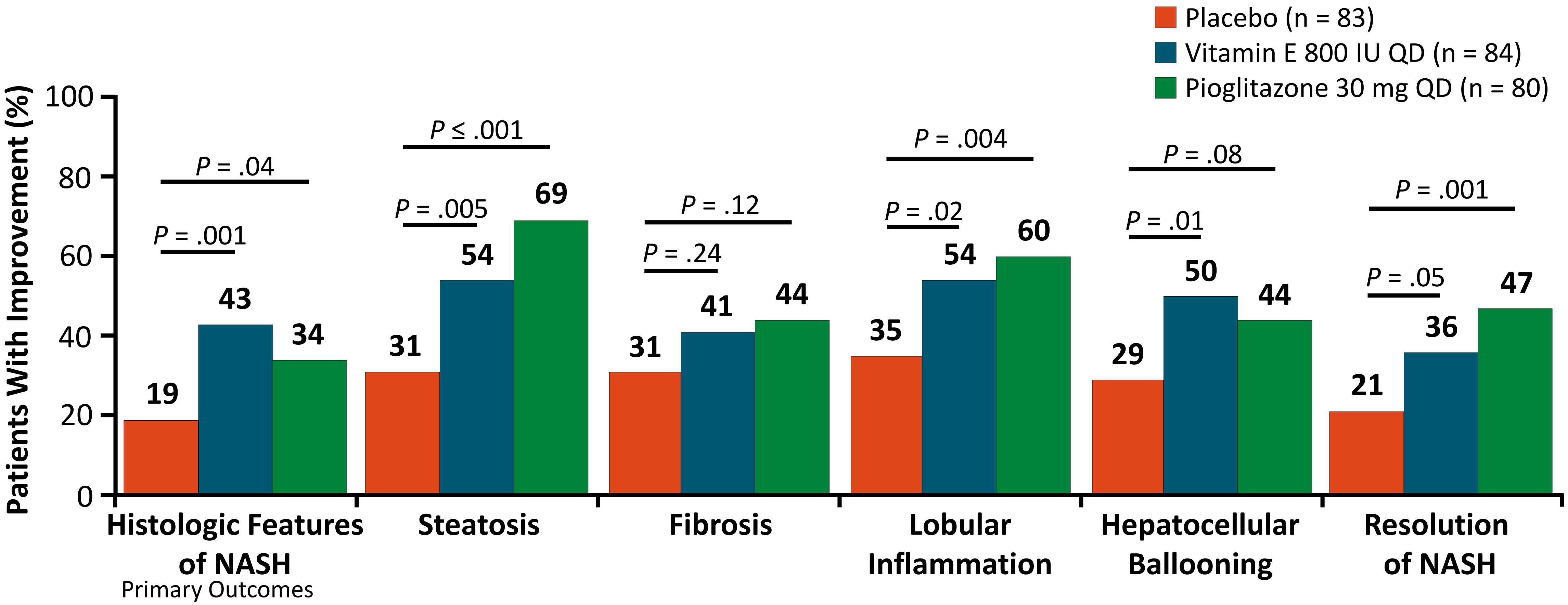
Targeting insulin resistance				
Compound	**Mechanism of action**	**Trial**	**Primary endpoint(s)**	**AASLD recommendation as NASH treatment**
Metformin	Multiple	Multiple studies	Various	Not recommended
Pioglitazone	PPARγ agonist	PIVENS* Multiple studies	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in patients with biopsy-proven NASH
Liraglutide	GLP-1 receptor agonist	LEAN*	Resolution of NASH without fibrosis worsening	Premature to consider GLP-1 receptor agonists

Targeting Oxidative stress				
Compound	**Mechanism of action**	**Trial**	**Primary endpoint(s)**	**AASLD recommendation as NASH treatment**
Vitamin E	Antioxidant	PIVENS* TONIC*	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in non-diabetic adults with biopsy-proven NASH

Adapted from Dr. Stephen Harrison's EASL2019 Presentation

Conclusions
Vitamin E was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes. There was no benefit of pioglitazone over placebo for the primary outcome; however, significant benefits of pioglitazone were observed for some of the secondary outcomes.

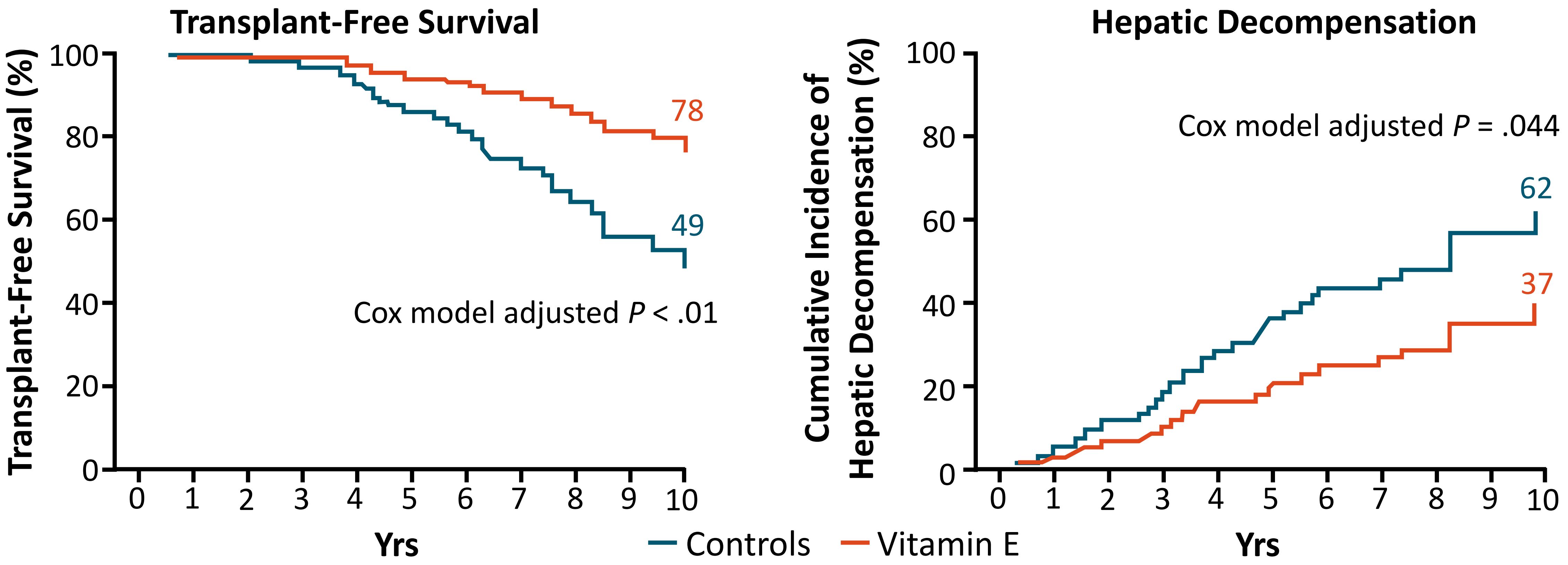
NASH and no diabetes or cirrhosis (N = 247)



Sanyal. NEJM. 2010;362:1675.

Vitamin E Improves Transplant-Free Survival and Hepatic Decompensation in Patients With NASH

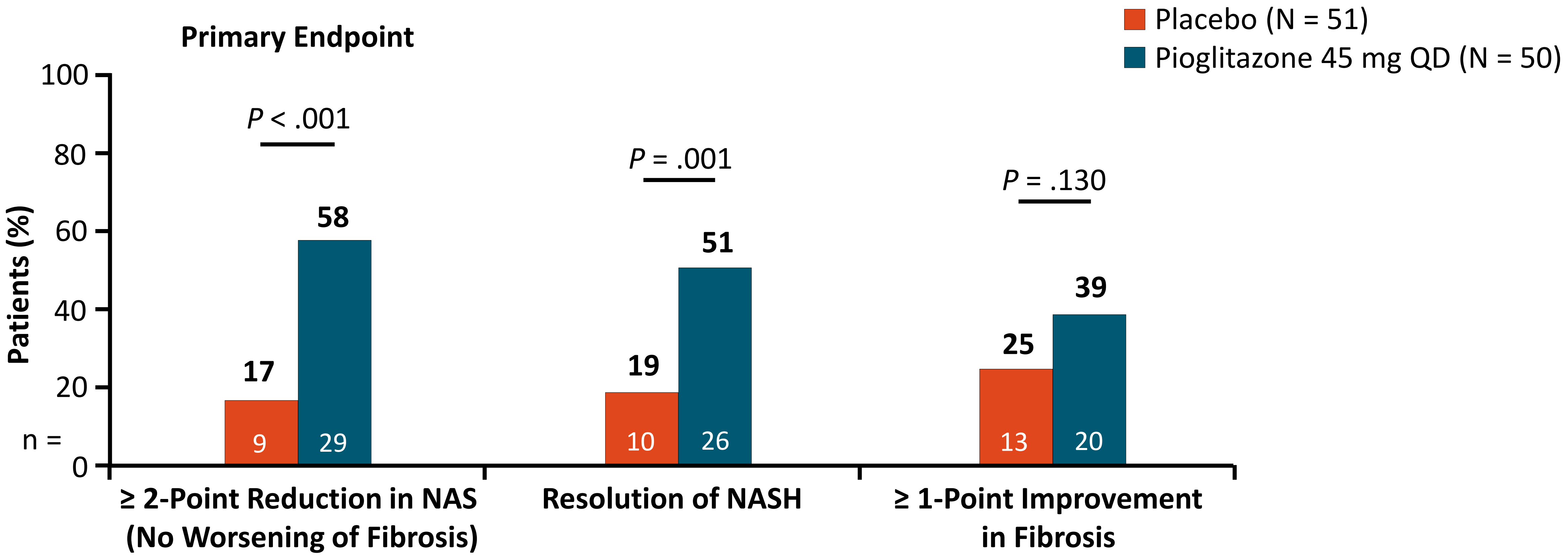
- Single-center study of patients with biopsy-proven NASH and bridging fibrosis or cirrhosis (N = 236) followed for median 5.62 yrs



Vilar-Gomez. Hepatology. 2019;[Epub].

TZD Pioglitazone in NASH and Prediabetes or Type 2 Diabetes: 18-Mo Outcomes

- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or type 2 diabetes (N = 101)[1]



Cusi. Ann Intern Med. 2016;165:305.

NAS:nonalcoholic fatty liver disease activity score

AASLD Guidance: Vitamin E

- **May be considered** to treat biopsy-proven NASH in **nondiabetic** adults
- At 800 IU/day improves liver histology but not fibrosis
- Risks and benefits should be discussed with each patient
  - Long-term safety issues concerns linger (eg, impact on long-term mortality, prostate cancer)
- **Not recommended** to treat NASH in **diabetic** patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
  - More data on safety and efficacy needed

Chalasani. Hepatology. 2018;67:328.

AASLD Guidance: Use of Insulin Sensitizers to Treat NAFLD/NASH

- **Metformin**
  - Not recommended for treating NASH in adults
  - Improves serum aminotransferases and IR, but does not significantly improve liver histology
- **GLP-1 RAs**
  - It is premature to consider GLP-1 RAs to specifically treat liver disease in patients with NAFLD or NASH
- **Pioglitazone** ✓
  - With biopsy-proven NASH: improves liver histology in patients **with and without T2D**
  - Risks and benefits should be discussed with each patient
  - Without biopsy-proven NASH: should not be used for NAFLD

Chalasani. Hepatology. 2018;67:328.

Currently Available Pharmacologic Agents (Off Label)

Targeting Insulin Resistance

Compound	Mechanism of Action	Trial	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Metformin	Multiple	Multiple studies	Various	Not recommended for NASH per se
Pioglitazone	PPARγ agonist	PIVENS Multiple studies	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in patients with biopsy-proven NASH
Liraglutide	GLP-1 receptor agonist	LEAN*	Resolution of NASH without fibrosis worsening	Premature to consider GLP-1 receptor agonists

Targeting Oxidative Stress

Compound	Mechanism of Action	Trial Name	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Vitamin E	Antioxidant	PIVENS TONIC	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in **nondiabetic** adults with biopsy-proven NASH

*Phase IIa/b.

Chalasani. Hepatology. 2018;67:328.

Safety and Tolerability of Recommended Therapies (Off Label)

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at > 800 IU/day[1]
- Increased hemorrhagic stroke risk[2]
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; P = .008)[3]

Pioglitazone

- Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]
- Risk of osteoporosis in women[5]
- Equivocal bladder cancer risk
  - Increased in some studies[6]
  - No association in most studies[7,8]

Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

1. Miller. Ann Intern Med. 2005;142:37. 2. Schurks. BMJ. 2010;341:c5702. 3. Klein. JAMA. 2011;306:1549.
4. Bril. Diabetes Care. 2017;40:419. 5. Yau. Curr Diab Rep. 2013;13:329. 6. Tuccori. BMJ. 2016;352:i1541.
7. Lewis. JAMA. 2015;314:265. 8. Davidson. Diabetes Complications. 2016;30:981.

Agenda

- ✓ Recommended Pharmacologic Therapies for NASH

- ✓ Pipeline Pharmacologic Therapies for NASH

Categorization of NASH Development Assets

Targeted Metabolic
- Insulin sensitizers (GLP-1)
- FGF21/19
- SGLT-1 inhibitors
- KHK inhibitor
- PUFAs
- IBAT inhibitors
- DGAT-2 inhibitors

ROS stress reduction
- Vitamin E
- mTOT inhibitors

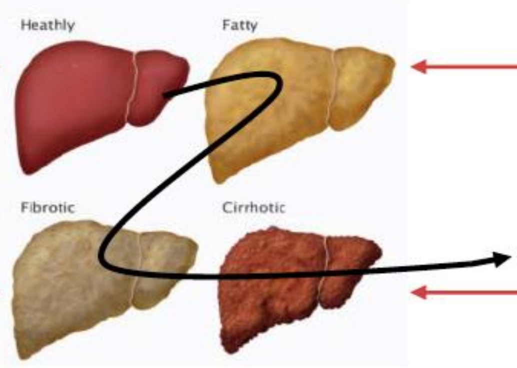
Anti-Steatosis
- ACC inhibitors
- SCD1 inhibitors
- FASN inhibitors
- Omega-3 fatty acid

Insulin Resistance

Metabolic Syndrome T2D

↑ lipids

Obesity



Nuclear Hormone Receptors

Multifactorial Metabolic
- PPAR agonists
- FXR agonists
- THRβ agonists
- LXR agonists
- Mito pyruvate carrier modulators

Intestinal permeability
- Larazotide
- Lubiprostone

Anti-Inflammatory/Fibrotic
- CCR2/5 inhibitor
- ASK-1 inhibitors
- Caspase inhibitors
- Galectin-3 inhibitors
- 5-lipogenase inhibitors
- CB1 inhibitors
- A3AR antagonists
- LOXL2 inhibitors
- NOX1/4 inhibitors
- ROCK2 inhibitors
- αvβ6/1 integrin inhibitors

Modified/Expanded from EASL2019 Phenex Presentation

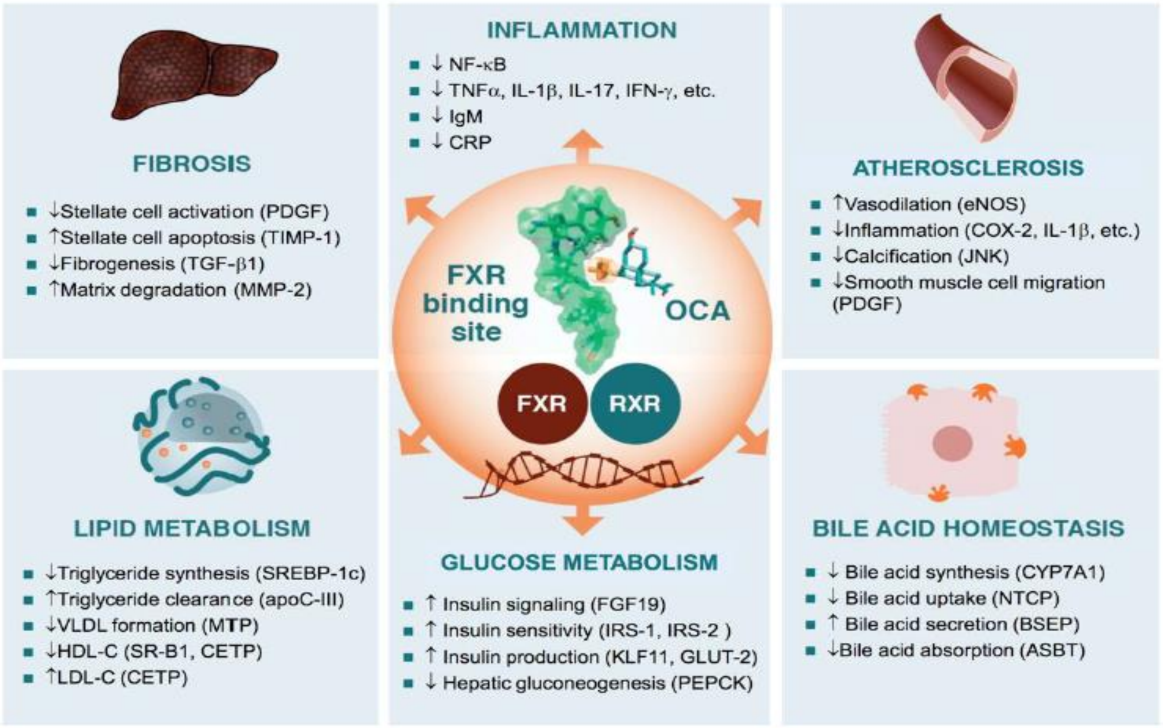
Treatment Options for NAFLD Patients: Compounds Presented at the AASLD Meeting

MoA	Type	Drug	Phase
Nuclear Hormone Receptor Agonist	FXR Agonist	OCA Tropifexor (LJN-452)	3 2b
	TRH-β Agonist	Resmetirom (MGL-3196)	2
	MPC Inhibitor	MSDC-0602K	2
	PPARα/γ Agonist	Saroglitazar Magnesium	2
Glucose Metabolism Pathway Modulator	SGLT-1/2 Inhibitor	Licogliflozin (LIK066)	2a
	GLP-1 Agonist	Cotadutide	2b
Lipid Metabolism Pathway Modulator	ACC Inhibitor	PF-05221304	2a
Apoptosis Signaling Regulator	ASK-1 Inhibitor	Selonsertib	3
	Caspase Inhibitor	Emricasan (IDN-6556)	2

Obeticholic Acid (OCA)

- Semi-synthetic bile acid (Chenodeoxycholic Acid) analogue
- FXR* agonist (liver and intestine receptor; role in enterohepatic circulation of BAs)
- FXR* is the key intracellular BA sensor regulating several metabolic processes involved in BA formation, transport and detoxification

Label for primary biliary cholangitis

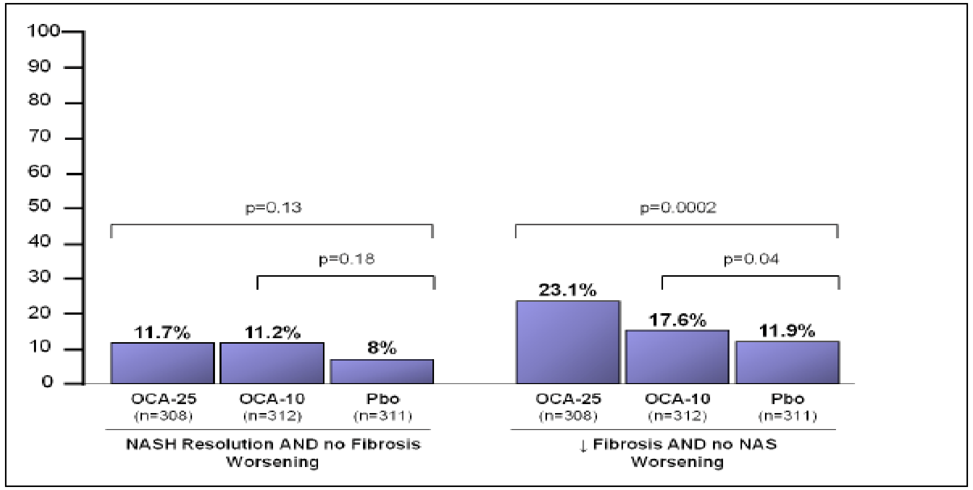


*FXR: Farnesoid X Nuclear Receptor

OCA – The REGENERATE Trial

Class	FXR Agonist
Phase	3
Patients	1,218 (24% F1#, 76% F2/F3)
Study Design	OCA 10 mg *vs.* 25 mg *vs.* Pbo
Tx Period	18 months; interim analysis*

F1 with at least one of the following: BMI ≥30, T2DM or ALT >1.5 ULN
* Planned Tx duration: 5 years (60 months)



Primary Endpoint	OCA 10 mg		OCA 25 mg		Placebo
	%	*P* Value*	%	*P* Value*	%
Fibrosis Improvement by ≥ 1 Stage†					
▪ ITT[1]	17.6	.04	23.1	.0002	11.9
▪ Expanded ITT[2]	15.7	.03	21.0	< .0001	10.6
NASH resolution‡					
▪ ITT[1]	11.2	.18	11.7	.13	8.0
▪ Expanded ITT[2]	11.3	.09	14.9	.0013	7.9

‡NASH resolution: Steatosis=0 OR Balooning=0 AND Inflammation=0/1

Younossi Z, et al. EASL 2019;GS-06

Sanyal AJ, et al. AASLD 2019;Abs#34

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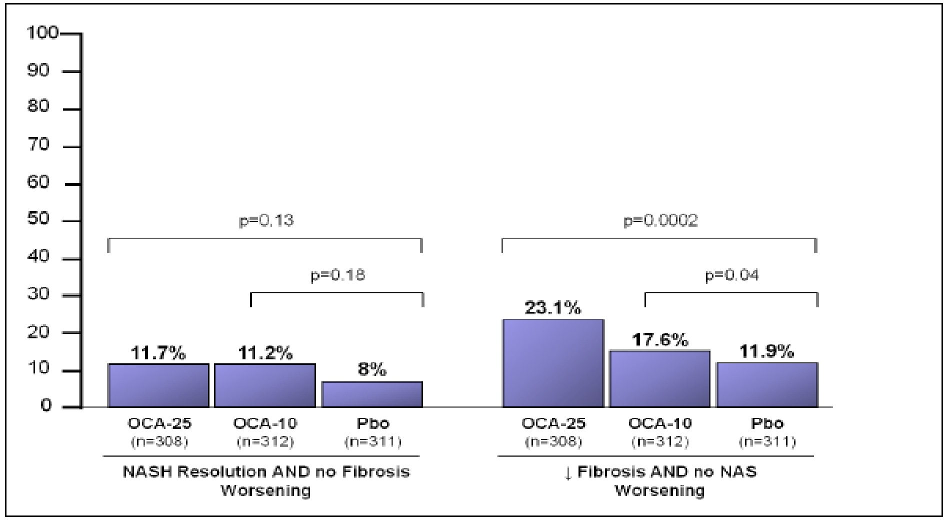

Events	OCA 10 mg (n = 407)	OCA 25 mg (n = 404)	Placebo (n = 407)
Pruritis, %	28	51	19
Deaths*, n	0	1	2
Gallstone-related events, %	1	3	< 1
Pancreatitis, %	< 1	< 1	< 1
Hepatic SAE, %	< 1	< 1	< 1
Cardiovascular AEs, %	7	6	5
▪ SAE	1	2	2

*Treatment unrelated

Younossi Z, et al. EASL 2019;GS-06

Sanyal AJ, et al. AASLD 2019;Abs#34

Tropifexor (LJN452, TXR) – The FLIGHT-FXR Trial

Class	FXR Agonist
Phase	2b (Part C)
Patients	152 (100% F2/F3)
Study Design	TXR 140 μg *vs.* 200 μg *vs.* Pbo
Tx Period	12 months; interim analysis*

* Planned Tx duration: 4 years (48 months)

Background

FLIGHT-FXR Trial Part A (n=77) and B (n=121)

Histological or Phenotypic (↑ ALT, BMI ≥27 and T2DM) diagnosis of NASH

- ✓ 60 and 90 μg (12 weeks)
- ✓ (10 and 30 μg also administered)
- ✓ ↓ steatosis (MRI-PDFF)
- ✓ ↓ inflammation (ALT)
- ✓ ↓ cholestasis ($_{\gamma}$GT)
- ✓ Favorable safety

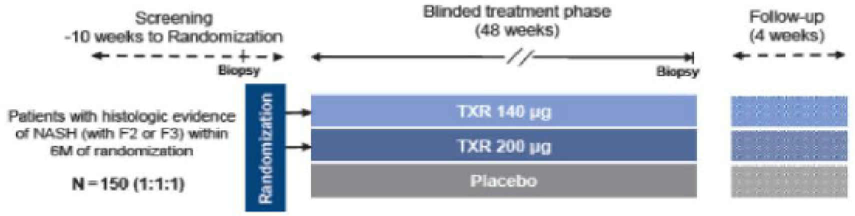

Table: LS means of absolute changes in ALT, GGT, and body weight, and relative change in hepatic fat fraction (HFF) from baseline to W12 estimated in repeated measures or ANCOVA models (FAS)

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

*Measured as magnetic resonance imaging-proton density fat fraction (MRI-PDFF). Data are presented as LS mean change (SE) with 2-sided P values reported for statistical significance
ALT, alanine aminotransferase; ANCOVA, analysis of covariance; FAS, full analysis set; GGT, gamma glutamyl transferase; HFF, hepatic fat fraction; LS, least square; SE, standard error; TXR, tropifexor

Sanyal AJ, et al. AASLD 2018;GS-06

Lucas KJ AJ, et al. AASLD 2019;Abs#L04

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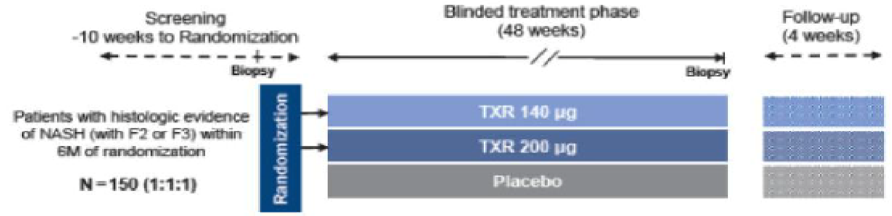
- ✓ ↓ steatosis (MRI-PDFF)
- ✓ ↓ inflammation (ALT)
- ✓ ↓ cholestasis (γGT)
- ✓ Favorable safety



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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

✓Pruritus
When reported, >60% grade 1
TD TXR-140 µg n=1 (2%), 200 µg n=3 (6%), Pbo 0%
✓↑ LDL
No TD or TXR reduction

Sanyal AJ, et al. AASLD 2018;GS-06

Lucas KJ AJ, et al. AASLD 2019;Abs#L04

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Resmetirom (MGL-3196) – The MGL-3196-05 Trial

Class	TRH-β° Agonist
Phase	2 (extension study)
Patients	31 (63% F2/F3*)
Study Design	80 mg (100 mg in 7)
Tx Period	36 weeks

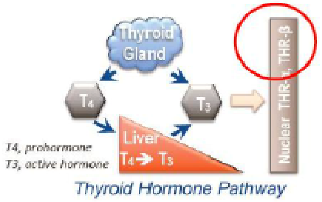
* Fibrosis assessed at week-36 biopsy (main study)

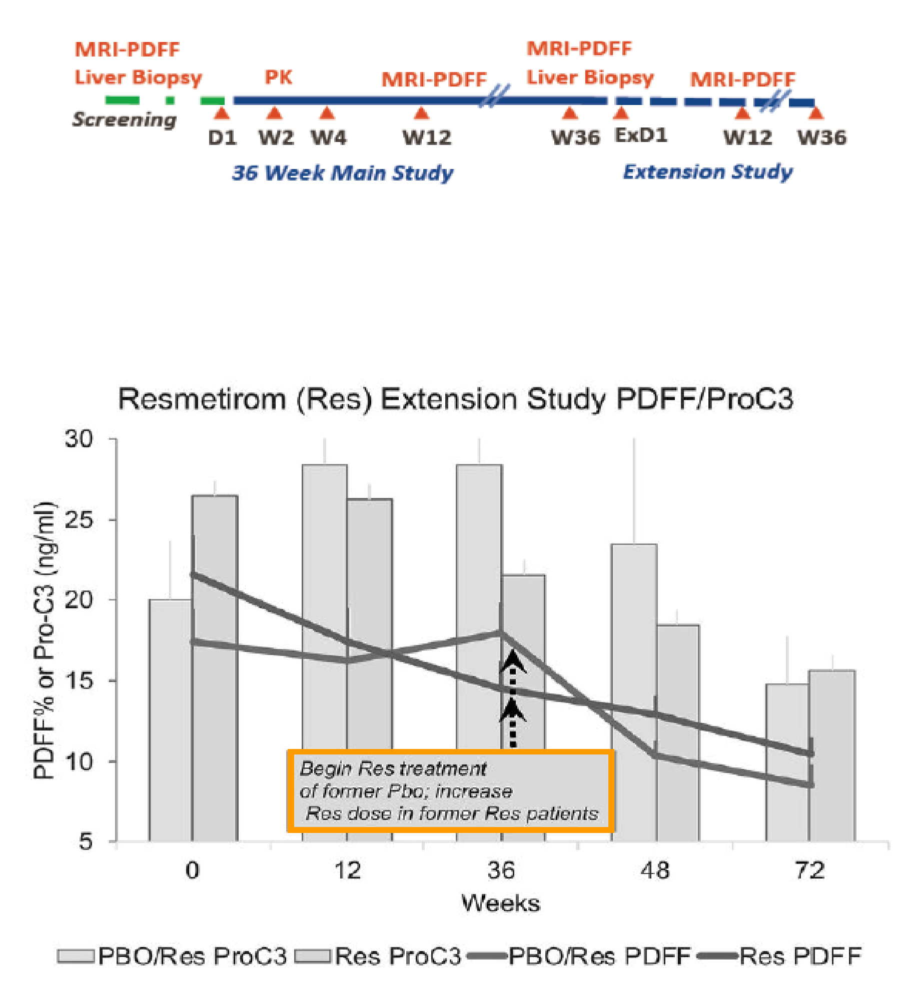
° Thyroid Receptor Hormone-β

Background

MGL-3196 80 mg (±20) vs. Pbo (36 weeks)

- ✓ ↓ steatosis (MRI-PDFF)
- ✓ ↓ ALT, AST and γGT
- ✓ ↓ Fibrosis biomarkers (ELF, Ck18, Pro-C3)
- ✓ ↓ LDL and TG





Harrison SA et al. AASLD 2018

Harrison SA, et al. AASLD 2019;Abs#263

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MRI-PDFF= Magnetic Resonance Imaging Proton Density Fat Fraction

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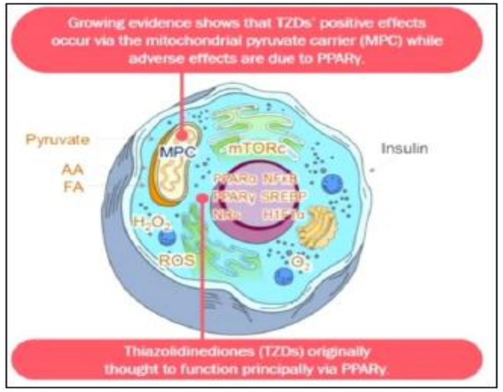
MSDC-0602K – The EMMINENCE Trial

Class	MPC° Inhibitor#
Phase	2b
Patients	392* (NAS >4, F1-F3**; 50% TDM)
Study Design	62.5 mg *vs.* 125 mg *vs.* 250 mg *vs.* Pbo
Tx Period	48 weeks

* 1,090 screened; **50% F2-F3

° Mithocondrial Piruvate Carrier



Background

#Second Generation Insulin Sensitizer

First Generation Insuline Sensitizers (Thiazolinediones; PPARγ Agonists) are characterized by SAE including weight gain, edema, bone fractures and hypoglicemia

- ✓ ↓ Insuline resistance
- ✓ ↓ Glc
- ✓ ↓ Liver inflammation and fibrosis (Pioglitazone)

#Second Generation TZD with poor direct binding to PPARγ but ability to modulate MPC (*Mithocondrial Piruvate Carrier*)

Harrison SA, et al. AASLD 2019;Abs#L01; Harrison SA, J Hepatol 2019, *in press*

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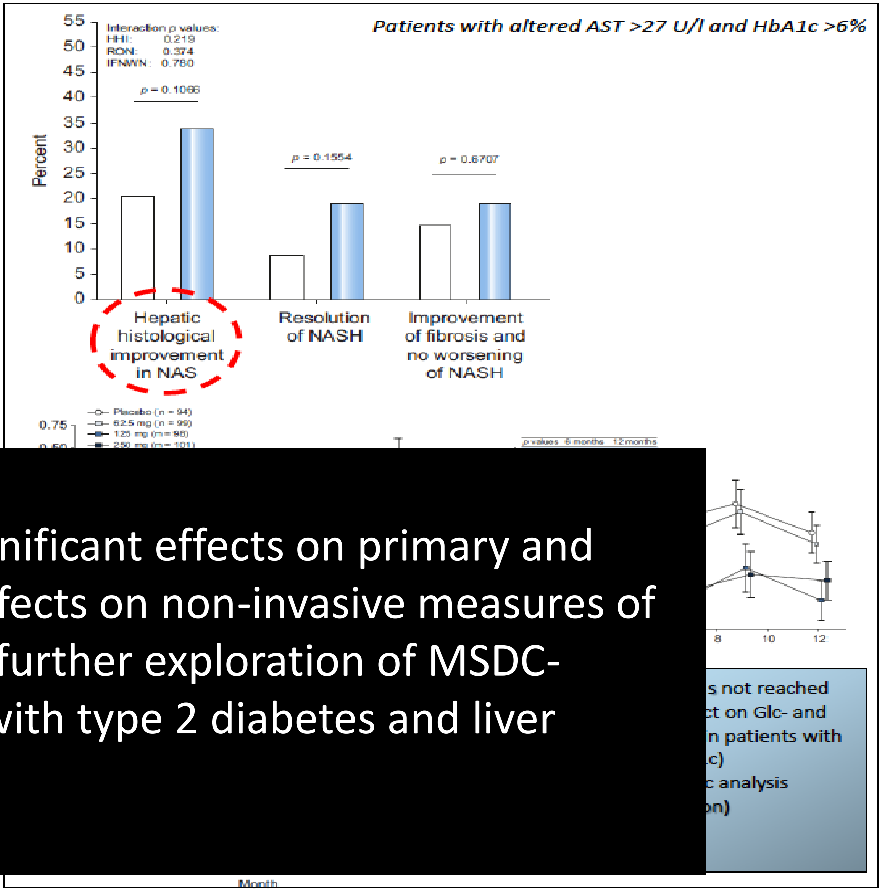

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Agonists)

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- ✓ ↓ I
- ✓ ↓ C
- ✓ ↓ L

CONCLUSIONS:
MSDC-0602K did not demonstrate statistically significant effects on primary and secondary liver histology endpoints. However, effects on non-invasive measures of liver cell injury and glucose metabolism support further exploration of MSDC-0602K's safety and potential efficacy in patients with type 2 diabetes and liver injury.

Harrison SA, et al. AASLD 2019;Abs#L01; Harrison SA, J Hepatol 2019, *in press*

(NAS) non-alcoholic fatty liver disease activity score

Saroglitazar – EVIDENCE IV Study

Class	PPARα/γ° Agonist*
Phase	2
Patients	106#
Study Design	Saro 1 mg *vs.* 2 mg *vs.* 4 mg *vs.* Pbo
Tx Period	16 weeks

* >1,000 fold selectivity for PPARα over PPARγ
\# NAFLD or NASH with ALT ≥50 U/l and BMI ≥25 Kg/m²
° Peroxysome Proliferator Activated Receptor α/γ

Background

- ✓ Marketing authorization in India (2013)
- ✓ Management of diabetic dyslipidemia and hypertrigliceridemia
- ✓ Phase 3 PRESS IV and PRESS V trials
- ✓ Real-world clinical studies; 4 mg for 12- 58 weeks
- ✓ ↓ TG, non-HDL Cho, HbA1c, ALT
- ✓ No safety issues

Table. Changes in efficacy endpoints in full analysis set population from baseline to week-16

Efficacy Endpoints	Saroglitazar 4 mg (n=27)	Saroglitazar 2 mg (n=23)	Saroglitazar 1 mg (n=26)	Placebo (n=28)
Primary Efficacy Endpoint				
Percentage change in ALT (U/L)	-44.39	-33.16	-27.31	4.16
**p* value	<.0001	<.0001	0.0002	
Secondary Efficacy Endpoints				
Absolute change in liver fat content (%) by MR-PDFF	-4.21	-0.42	0.53	-0.31
**p* value	0.01	0.94	0.59	
% of patients with reduction in liver fat content by > 10%	55.56	28.57	23.08	28.00
**p* value	0.04	0.97	0.69	
% of patients with reduction in liver fat content by > 30%	40.74	4.76	11.54	8.00
**p* value	0.0069	0.85	0.52	
% change in weight (kg)	1.88	1.73	2.39	0.28
**p* value	0.99	0.54	0.33	

**p* value derived from comparison between Saroglitazar 4 mg vs placebo, Saroglitazar 2 mg vs placebo, and Saroglitazar 1 mg vs placebo

<u>Other reached end-points (Saro 4 mg):</u>
- ↓ HOMA-IR
- ↓ TG
- ↓ Cho
- ↓ APRI

Saroglitazar Magnesium 4 mg significantly improved serum ALT, hepatic steatosis, insulin resistance, and dyslipidemia in patients with NAFLD/NASH.

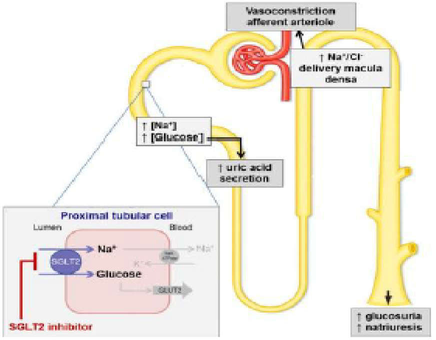
Kaul U, et al. Cardiovasc Diabetol 2019

Gawrieh S, et al. AASLD 2019;Abs#L010

Licogliflozin (LIK066)

Class	SGLT§-1/2 Inhibitor
Phase	2a
Patients	110* (77 completed treatment)
Study Design	30 mg (n=25) *vs.* 150 mg (n=34) *vs.* Pbo (n=18)
Tx Period	12 weeks; interim analysis (# pts)

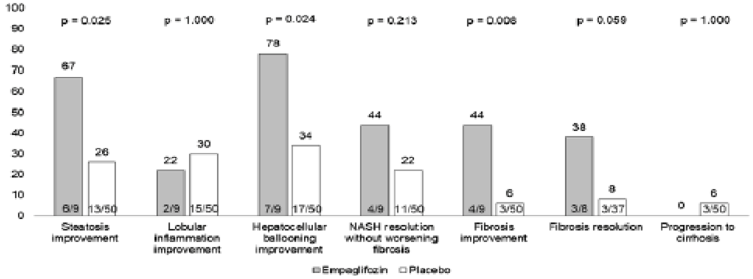
* Histological or Phenotypic# diagnosis of NASH
\# BMI ≥ 27 Kg/m² (non-Asians) or ≥23 Kg/m² (Asians) and ALT ≥50 U/l (males) or ≥35 (females) and T2DM



§Sodium-Glucose Co-Transporter

Background

- ✓ Pilot Study (NCT02964715) with **Empagliflozin (24w)**
- ✓ NASH, F0-F3, HbA1c >6.5%



	30 mg	150 mg
↓ ALT **	19% (p=ns)	27% (p=0.036)
↓γGT **	26% (p=0.014)	32% (p=0.001)
↓ Body Weight **	~4% (p=0.0001)	~4% (p=0.0001)
Liver fat **	10% (p=ns)	22% (p=0.01)
Diarrhea	40% (p=ns)	76.5%

**Relative reductions *vs.* Placebo

Lai LL, et al. Dig Dis Sci 2019

Harrison SA, et al. AASLD 2019;Abs#L07

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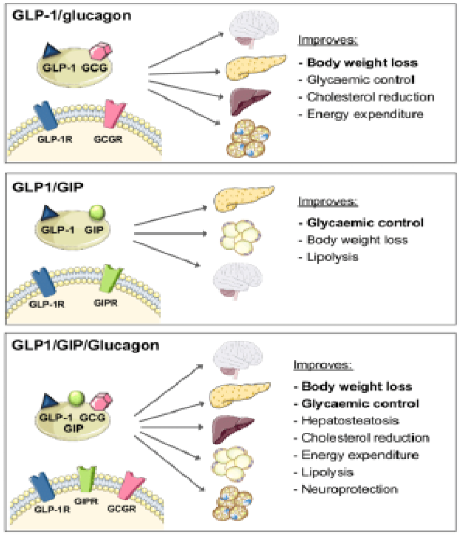
Cotadutide (MEDIO382)

Class	GLP-1° Analogue + Glucagon Activity
Phase	2b
Patients	834* (689 with available data)
Study Design	COT 100 µg *vs.* 200 µg *vs.* 300 µg *vs.* Pbo *vs.* LIR#
Tx Period	26 weeks

* T2DM, BMI ≥25 Kg/m², on metformin

° Glucagone-like Peptide-1



Background

✓ Pha

✓ ↓ H

Lirag

Conclusion: Superior reductions in bodyweight, ALT AST levels were observed with cotadutide vs liraglutide

Despite not being validated for interventions, improvements in FLI and NFS with cotadutide may indicate reduced liver fat and fibrosis, respectively. These data support prospective clinical trials with cotadutide for a NASH indication

95% CI vs placebo vs liraglutide	-18.4, 1.1 P=0.006 P=0.951	-11.9, 0.2 P=0.005 P=0.551	-16.8,-4.3 P<0.001 0.779	-17.6, -0.5 P=0.003 –	0.9, 18.8 – –

#Armstrong MJ, et al. Lancet 2016

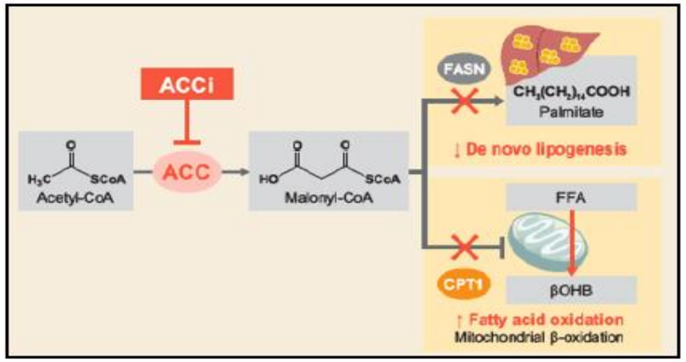
Nahara R, et al. AASLD 2019;Abs#35

UNIVERSITÀ DI PAVIA

nonalcoholic fatty liver disease fibrosis score (NFS) and fatty liver index (FLI)

PF05221304

Class	ACC° Inhibitor
Phase	2a *(dose ranging)*
Patients	305 (68% with presumed NASH*)
Study Design	2 mg *vs.* 10 mg *vs.* 25 mg *vs.* 50 mg *vs.* Pbo
Tx Period	16 weeks



* Including BMI ≥25 Kg/m2 and MRI-PDFF ≥8% and Met-S

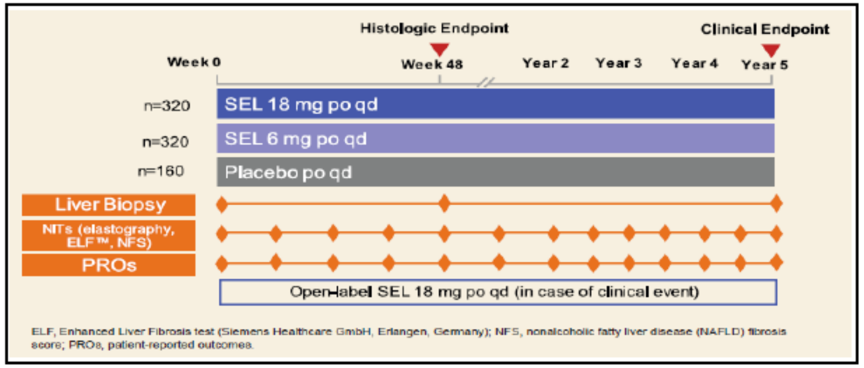
Randomized Treatment (N, subjects randomized per arm)	Placebo (N=61)	PF'1304 (administered once-daily, QD)			
		2 mg (N=63)	10 mg (N=62)	25 mg (N=58)	50 mg (N=61)
Efficacy-Related Endpoints					
Liver fat by MRI-PDFF*	-7.2 (-13.9, 0.0)	-17.1 (-22.7, -11.1)	-49.9 (-53.3, -46.2)	-55.9 (-59.0, -52.4)	-64.8 (-67.5, -62.0)
• *Relative reduction of ≥ 30%*#	*3 (6)*	*13 (22)*	*42 (74)*	*47 (87)*	*45 (90)*
• *Absolute reduction to ≤ 5%*#	*0*	*2 (3)*	*8 (14)*	*13 (24)*	*18 (36)*
ALT*^	-8.5 (-15.2, -1.2)	-12.5 (-18.7, -5.8)	-27.7 (-32.9, -22.2)	-31.3 (-36.6, -25.5)	-46.8 (-50.8, -42.4)
Safety-Related Endpoints					
Subjects prematurely withdrawn (n=42; 14%)	7	5	7	10	13
• *For adverse event*	*3*	*3*	*2*	*6*	*9*
Fasting Serum TG*	4.8 (-3.0, 13.3)	11.0 (3.3, 19.3)	59.2 (48.0, 71.2)	86.8 (72.9, 101.9)	112.1 (96.2, 129.3)
Platelet count*	1.3 (-1.2, 4.0)	-3.1 (-5.5, -0.8)	-6.8 (-9.0, -4.5)	-9.2 (-11.6, -6.9)	-8.5 (-10.8, -6.1)
AST*^	-6.6 (-12.9, 0.1)	-7.0 (-13.0, -0.7)	-16.8 (-22.2, -11.0)	-15.6 (-21.5, -9.3)	-35.5 (-40.0, -30.7)
Alkaline Phosphatase*^	-0.8 (-3.8, 2.2)	2.3 (-0.6, 5.3)	6.9 (3.9, 10.1)	15.5 (11.9, 19.1)	19.3 (15.7, 23.0)
GGT*^	-7.7 (-13.9, -1.2)	0.1 (-6.3, 7.1)	4.9 (-1.9, 12.2)	21.5 (13.0, 30.6)	11.1 (3.6, 19.3)
Direct LDL-C*	4.2 (-1.8, 10.6)	-1.1 (-6.5, 4.6)	-8.6 (-13.6, -3.3)	-11.1 (-16.3, -5.6)	-20.2 (-24.9, -15.3)
HDL-C*	2.8 (-1.3, 6.9)	-4.2 (-7.7, -0.6)	-15.1 (-18.2, -11.9)	-23.6 (-26.6, -20.5)	-23.9 (-26.9, -20.8)
Total Cholesterol*	3.5 (0.5, 6.6)	-1.3 (-4.0, 1.4)	4.1 (1.2, 7.0)	4.9 (1.8, 8.0)	3.1 (0.1, 6.2)
HbA1c*	0.03 (-0.03, 0.10)	-0.04 (-0.10, 0.02)	-0.11 (-0.17, -0.05)	-0.20 (-0.27, -0.14)	-0.34 (-0.40, -0.27)

*Mixed-model-repeated-measures method with treatment, time, treatment-by-time interaction as fixed effects, subject as random effect, and baseline as covariate with results reported as least-square means (80% confidence interval; CI) for percent change from baseline at Week 16 for all parameters *except* HbA1c which is presented as change from baseline; values are statistically significantly different from placebo when 80% CI excludes zero
#Represents number (percent) of subjects who achieve these thresholds, at end of dosing
^Limited to sub-set with (presumed) NASH

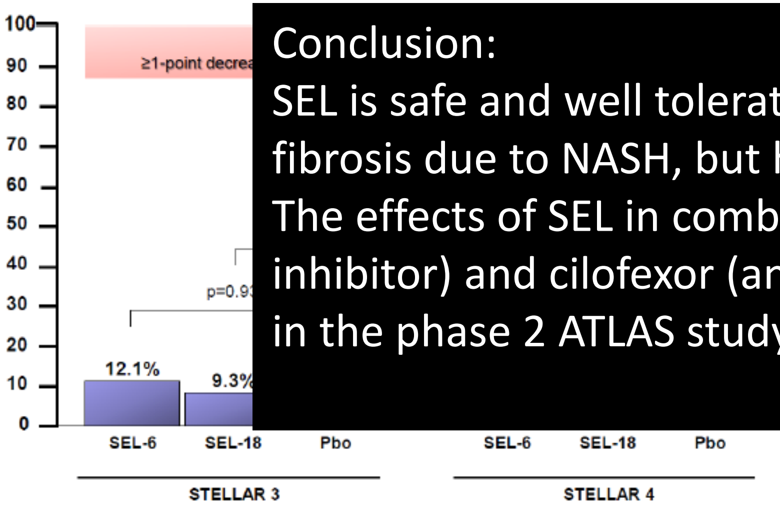
Selonsertib – The STELLAR-3 and 4 Studies

Class	ASK1° Inhibitor
Phase	3
Patients	803 F3 and 877 F4
Study Design	SEL 18 mg *vs.* 6 mg *vs.* Pbo
Tx Period	48 weeks

° Apoptosis Signal-regulating Kinase 1



At a pre-planned efficacy analysis at week 48, both studies were stopped due to lack of efficacy.



Conclusion:
SEL is safe and well tolerated in patients with advanced fibrosis due to NASH, but has no efficacy as monotherapy.
The effects of SEL in combination with firsocostat (an ACC inhibitor) and cilofexor (an FXR agonist) are being evaluated in the phase 2 ATLAS study

			lacebo N=159)	P-value 18 mg vs. placebo	P-value 6 mg vs. placebo
			13.2 4, 19.5)	0.42	0.93
			8.2 5, 13.7)	0.34	0.20
			15.7 .4, 22.3)	0.26	0.81
			lacebo N=172)	P-value 18 mg vs. placebo	P-value 6 mg vs. placebo
CI)			12.8 2, 18.7)	0.56	1.00
NASH resolution without worsening of fibrosis, % (95% CI)	2.3 (1.0, 4.4)	3.4 (1.8, 5.9)	4.1 (1.7, 8.2)	0.37	0.76

Gilead Press Release, April 2019

Harrison SA, et al. AASLD 2019;Abs#64

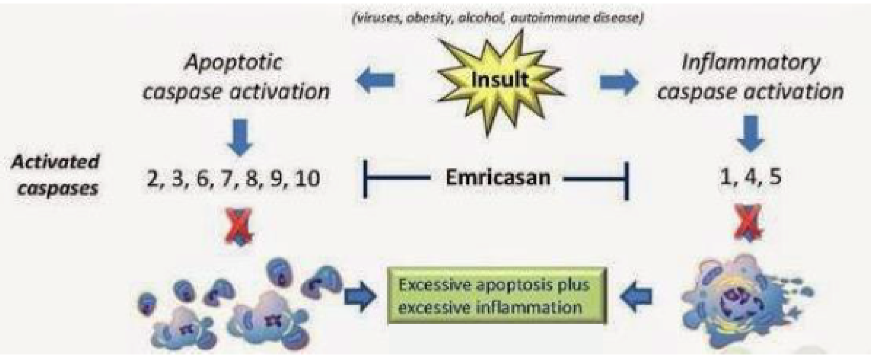
Fondazione IRCCS Policlinico San Matteo

Sistema Socio Sanitario Regione Lombardia

Emricasan (IDN-6556) – The ENCORE (NF) Study

Class	Caspase Inhibitor
Phase	2
Patients	318 (NAS ≥4 and F 1-3)*
Study Design	5 mg *vs.* 50 mg *vs.* Pbo (TD)
Tx Period	72 weeks

* Treatment completion in 286 (89%)



Background

HEPATOLOGY
AASLD

HEPATOLOGY, VOL. 69, NO. 2, 2019 LIVER FAILURE/CIRRHOSIS/PORTAL HYPERTENSION

Emricasan (IDN-6556) Lowers Portal Pressure in Patients With Compensated Cirrhosis and Severe Portal Hypertension

Guadalupe Garcia-Tsao,[1] Michael Fuchs,[2] Mitchell Shiffman,[3] Brian B. Borg,[4] Nikolaos Pyrsopoulos,[5] Kirti Shetty,[6] Juan F. Gallegos-Orozco,[7] K. Rajender Reddy,[8] Eyob Feyssa,[9] Jean L. Chan,[10] Mason Yamashita,[10] James M. Robinson,[10] Alfred P. Spada,[10] David T. Hagerty,[10] and Jaime Bosch[11,12]

Conclusion: Despite signs of target engagement with decreases in ALT and caspase 3/7, treatment with an oral caspase inhibitor did not meet the primary and secondary endpoints of fibrosis improvement or NASH resolution in patients with NASH and fibrosis.

Garcia-Tsao G, et al. Hepatology 2019

Harrison SA, et al. AASLD 2019;Abs#61

Fondazione IRCCS Policlinico San Matteo

Sistema Socio Sanitario Regione Lombardia

Summary

	#Pts	Treatment Duration (months)	Histology	MRI-PDFF	ALT	AST	γGT	Cho	TG	BMI	AE
OCA	1,218	18	Reached	-	Reached	Reached	Reached	↑ LDL	-	-	Pruritus
TRO	152	12	To be assessed	Reached	Reached (200 μg)	-	Reached	↑ LDL	-	Reached	Pruritus (ns)
MGL-3196	31	9	Inclusion criteria	Reached	Reached	Reached	Reached	↓ LDL	-	-	Rare (ns)
MSDC	392	12	Not reached	-	Reached (125, 250 mg)	Reached (125 mg)	Reached (250 mg)	Not Reached	Not Reached	↑	Rare (ns)
Saroglitazar	106	4	-	Reached	Reached	-	-	↓ Cho	Reached	Not reached	-
Licogliflozin	110	3	Inclusion criteria	Reached (150 mg)	Reached	Reached	Reached	-	-	Reached	Diarrhea (150 mg)
Cotadutide	77	6	-	Reached (FLI index)	Reached (200, 300 μg)	Reached (300 μg)	Reached	-	-	Reached	-
PF-05221304	305	4	-	Reached (entire cohort)	Reached (NASH)	-	-	-	-	-	-
Selonsertib	1,680	12	Not reached	-	Not reached	Not reached	Not reached	-	-	-	Rare (ns)
Emricasan	318	18	Not reached	-	Reached	Not reached	-	-	-	-	>85% (ns)

Conclusions

- ✓ Several compounds are under investigation for the treatment of NAFLD patients
- ✓ Most data come from Phase 2 trials, including interim analysis, while no follow-up data have been presented regarding drugs in more advanced stages of clinical development
- ✓ Most studies include limited number of NAFLD patients, receiving treatment for shorter than expected duration
- ✓ In all studies, surrogate endpoints have been used
- ✓ With all these caveats, experimental drugs seem to be safe and well tolerated
- ✓ Further data are warrented to assess both efficacy and safety of these new anti-NASH molecules