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Pharmacological treatment of NASH

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Disclosure

Gilead Sciences, and Intercept Pharmaceuticals, Inc.

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Agenda

- **Current Approaches for NASH**
  - Pioglitazone
  - Vitamin E
  - AASLD Guidance
- **Emerging Approaches**
  - Phase II
  - Phase III
- **Perspectives**

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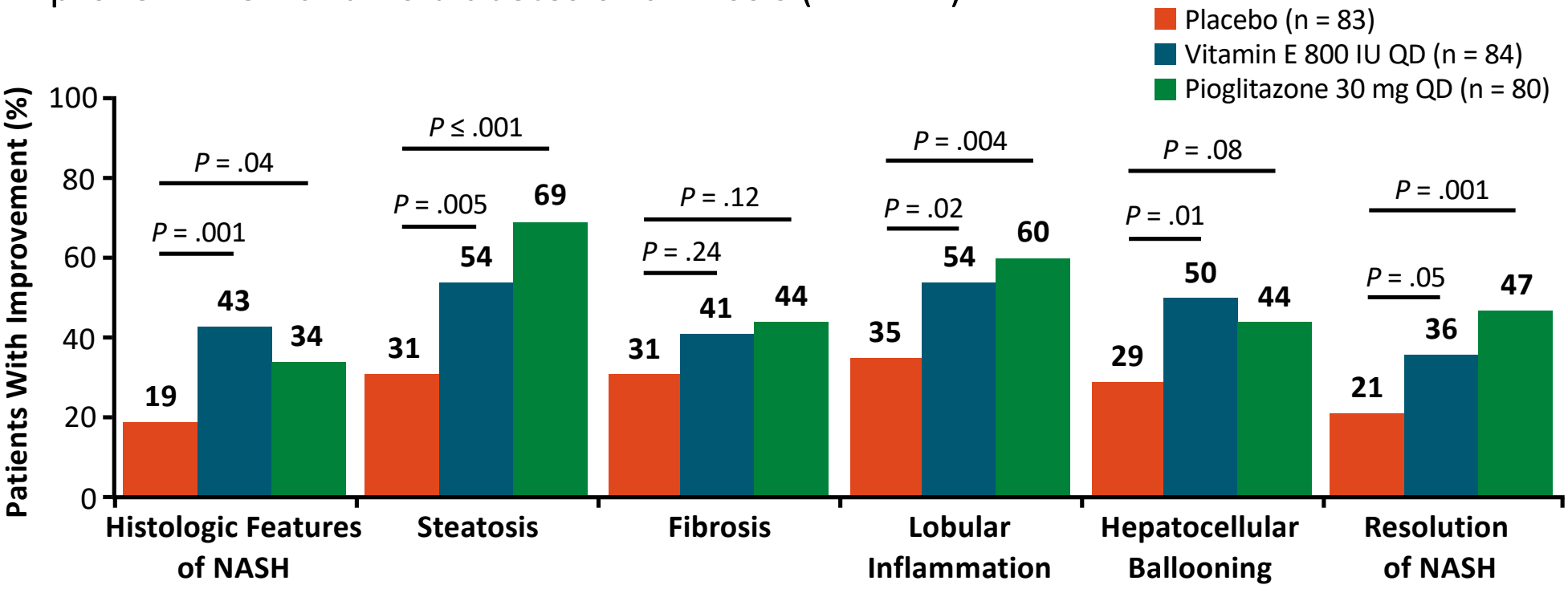
PIVENS: 96-Wk Results of Pioglitazone and Vitamin E in Patients With NASH

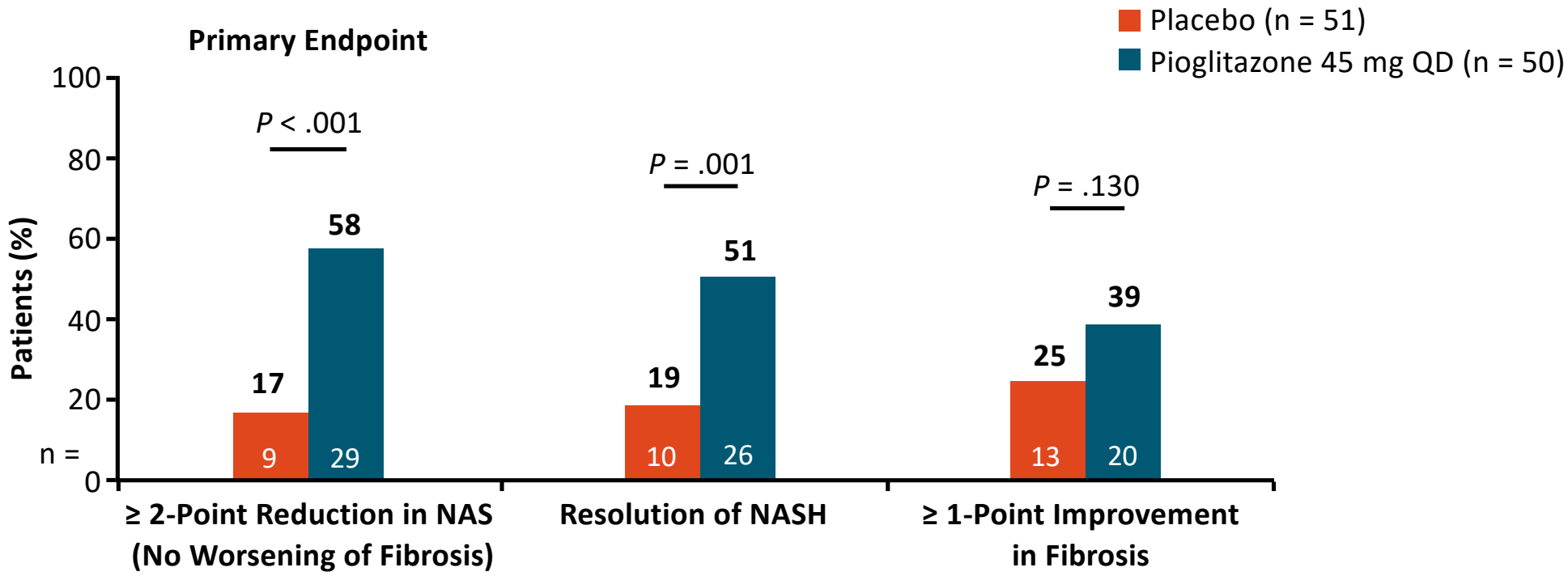
- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Sanyal. NEJM. 2010;362:1675.

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

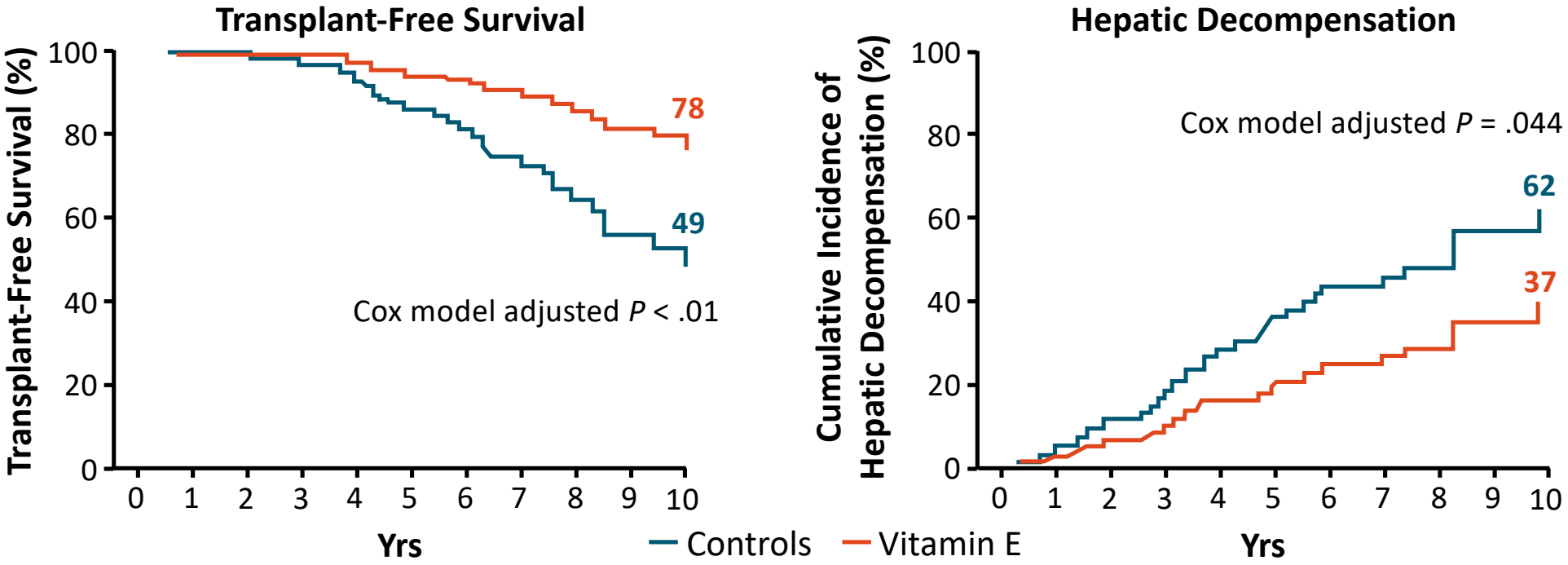
- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or type 2 diabetes (N = 101)[1]



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

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 of 5.62 yrs



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

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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 select 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.

AASLD Guidance: Treatment of NASH (Off-label)

- **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 treat liver disease specifically in patients with NAFLD or NASH
- **Pioglitazone** ✓
  - With biopsy-proven NASH: improves liver histology in patients **with and without T2D**
  - Without biopsy-proven NASH: should not be used for NAFLD
- **Vitamin E** ✓
  - With biopsy-proven NASH: may be used in patients **without T2D**
- **Risks and benefits should be discussed with each patient**

Chalasani. Hepatology. 2018;67:328.

Approaches for Currently Available Treatments

Weight loss[1-3]

- Lifestyle (diet, physical activity)
- Weight loss medications
- Bariatric surgery

In patients with advanced liver disease, choose or dose drugs appropriately.

Treat T2D and CV risk factors[4,5]

- Hyperglycemia (GLP-1 RA and/or SGLT-2i)
- Hypertension
- Dyslipidemia*

*NAFLD does not increase statin risk of drug-induced liver injury.[8]

Liver-directed treatment

- Vitamin E (except in diabetes)[6]
- Pioglitazone[6,7]

1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Sanyal. NEJM. 2010;362:1675. 7. Cusi. Ann Intern Med. 2016;165:305. 8. Bril. J Clin Endocrinol Metab. 2017;102:2950.

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Emerging Treatment Options for NASH

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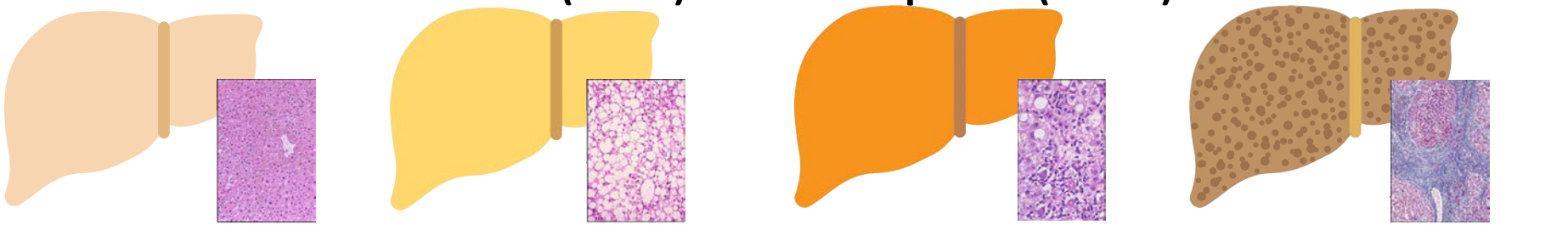
Examples of NASH Treatments in Phase II or III Investigations

NAFLD

Normal Liver | **Steatosis (NAFL)** | **Steatohepatitis (NASH)** | **Cirrhosis**



Insulin resistance and/or lipid metabolism → **Lipotoxicity and oxidative stress** → **Inflammation and immune activation** → **Cell death (apoptosis and necrosis)** → **Fibrogenesis and collagen turnover**

PPARγ:	Pioglitazone
GLP-1:	Liraglutide, semaglutide
SGLT:	Empagliflozin, licogliflozin, canagliflozin
DPP-4	Sitagliptin
ACC:	GS-0976, PF-05221304
SCD1:	Aramchol
ASBT:	Volixibat

PPARα/∂:	Elafibranor
PPARα/γ:	Saroglitazar
Pan-PPAR:	Lanifibranor
FGF19:	NGM282
FGF21:	Pegbelferim
FXR:	OCA, cilofexor, tropifexor, nidufexor
MPC:	MSDC-0602K
TGR-5:	INT-767/777
THR-β:	MGL-3196, VK2809

CCR2/5: Cenicriviroc (inflammatory target but affects fibrosis)

AOC3:	BI-1467335
P2X7R:	SGM-1019
TLR-4:	JKB-121/122

ASK1: Selonsertib (cell death target but affects fibrosis)

Caspase:	Emricasan

Galectin:	GR-MD-02
LOXL2:	Simtuzumab

Some agents have multiple targets

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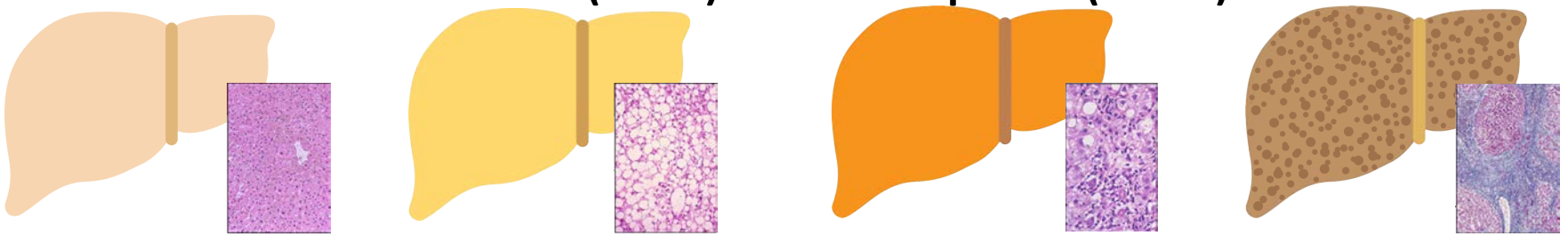

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Not proceeding forward

Some agents have multiple targets

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Phase III

Some agents have multiple targets

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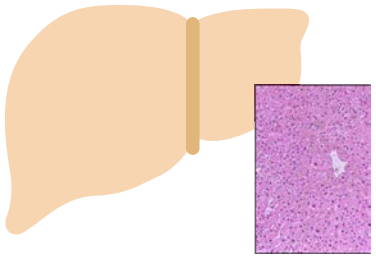
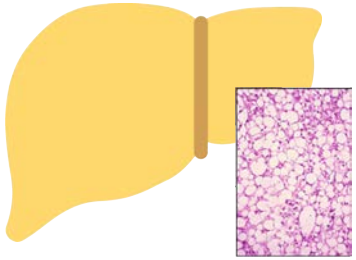
The NAFLD Continuum

NAFLD

Normal Liver

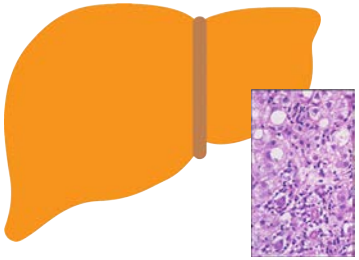


Steatosis "NAFL"



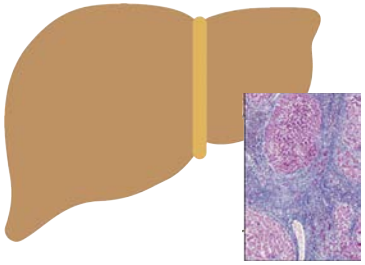
Fat infiltration ≥ 5% without ballooning, with or without inflammation

Steatohepatitis "NASH"



Fat infiltration ≥ 5% with necroinflammation and hepatocellular injury (ballooning, hepatocyte degeneration, Mallory bodies, or megamitochondria)

Cirrhosis



Increasing fibrosis, leading to cirrhosis

HCC

Chalasani. Hepatology. 2018;67:328.

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FDA: Liver Histologic Improvement Endpoints Likely to Predict Clinical Benefit

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

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

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NASH Treatments in Phase III Investigations

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NASH Treatments Currently in Phase III Investigations

Agent	MoA	Trial	N	Primary Endpoint(s)	Time Point
Cenicriviroc	CCR2/5 antagonist	AURORA[1]	2000	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Elafibranor	PPARα/σ agonist	RESOLVE-IT[2]	2000	Resolution of NASH with no fibrosis worsening	72 wks
Obeticholic acid	FXR agonist	REGENERATE[3]	931	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	18 mos
		REVERSE[4]	900	≥ 1 stage fibrosis improvement with no NASH worsening	18 mos
Resmetirom	THR-β agonist	MAESTRO-NASH[5]	2000	Resolution of NASH	52 wks
Aramchol	SCD1 inhibitor	ARMOR[6]	2000	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	52 wks

Phase III/IV studies use adaptive design

- Histologic endpoints for Subpart H conditional approval
- Clinical endpoints for full approval

1. NCT03028740. 2. NCT02704403. 3. Younossi. Lancet. 2019;394:2184. 4. NCT03439254. 5. NCT03900429. 6. NCT04104321.

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Cenicriviroc

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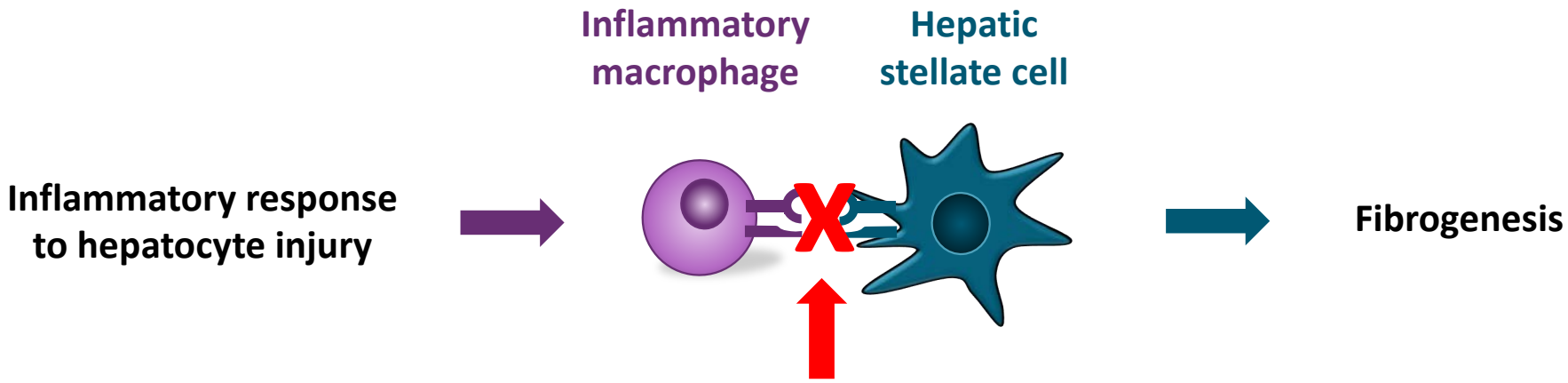
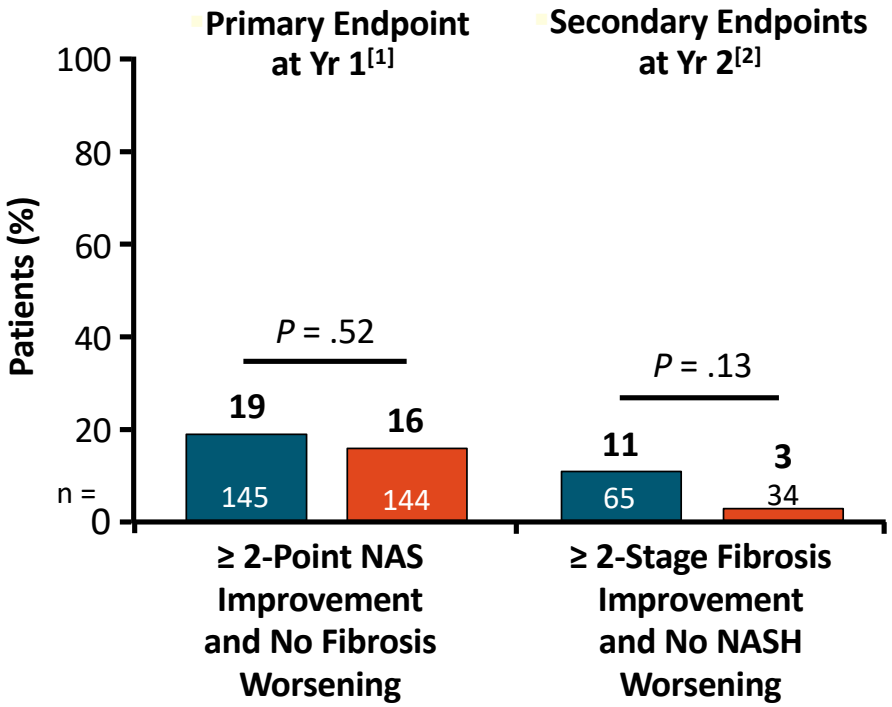
Cenicriviroc: CCR2/CCR5 Inhibitor

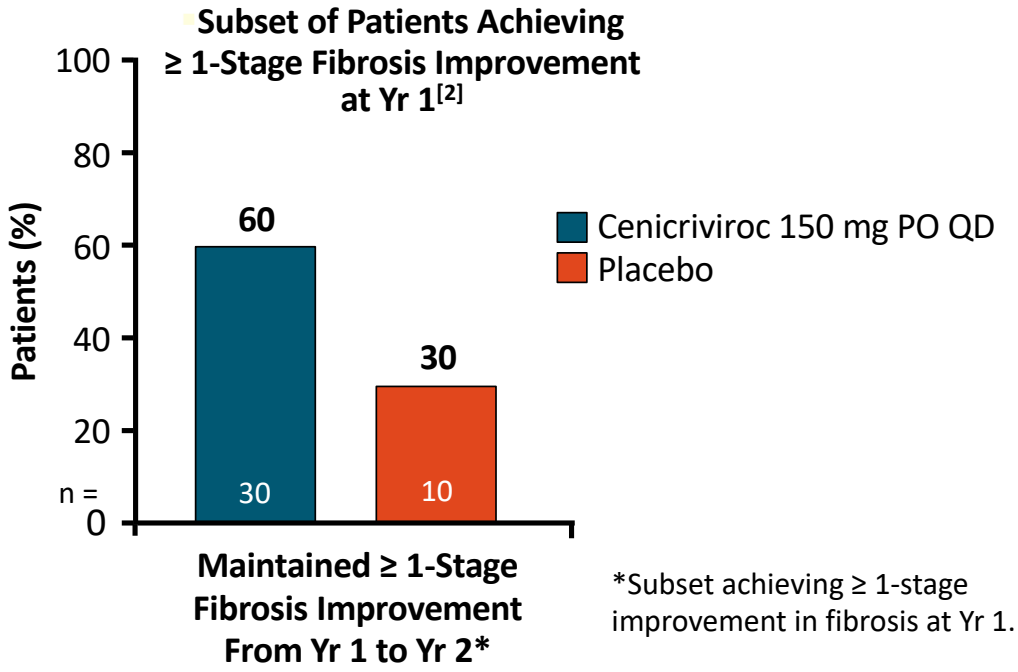


Friedman. Hepatology. 2018;67:1754.

CENTAUR: Cenicriviroc vs Placebo in Patients With NASH at Yr 1 and Yr 2

- International, randomized, double-blind, phase IIb study in patients with NASH, NAS ≥ 4, and F1-F3 fibrosis (N = 289)[1]





*Subset achieving ≥ 1-stage improvement in fibrosis at Yr 1.

1. Friedman. Hepatology. 2018;67:1754. 2. Ratziu. Hepatology. 2019. [Epub].

CENTAUR: Cenicriviroc Safety at Yr 2

- No clinically meaningful difference in overall incidence of AEs vs placebo
- Most AEs mild to moderate
- No deaths or study drug-related treatment-emergent serious AEs
- Drug-related AEs of grade ≥ 2 in ≥ 2% of patients occurred in 8.3% and 5.0% in cenicriviroc and placebo arms, respectively
- Serious AEs or ALT elevation no higher in cenicriviroc vs placebo

Ratziu. Hepatology. 2019. [Epub].

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Elafibranor

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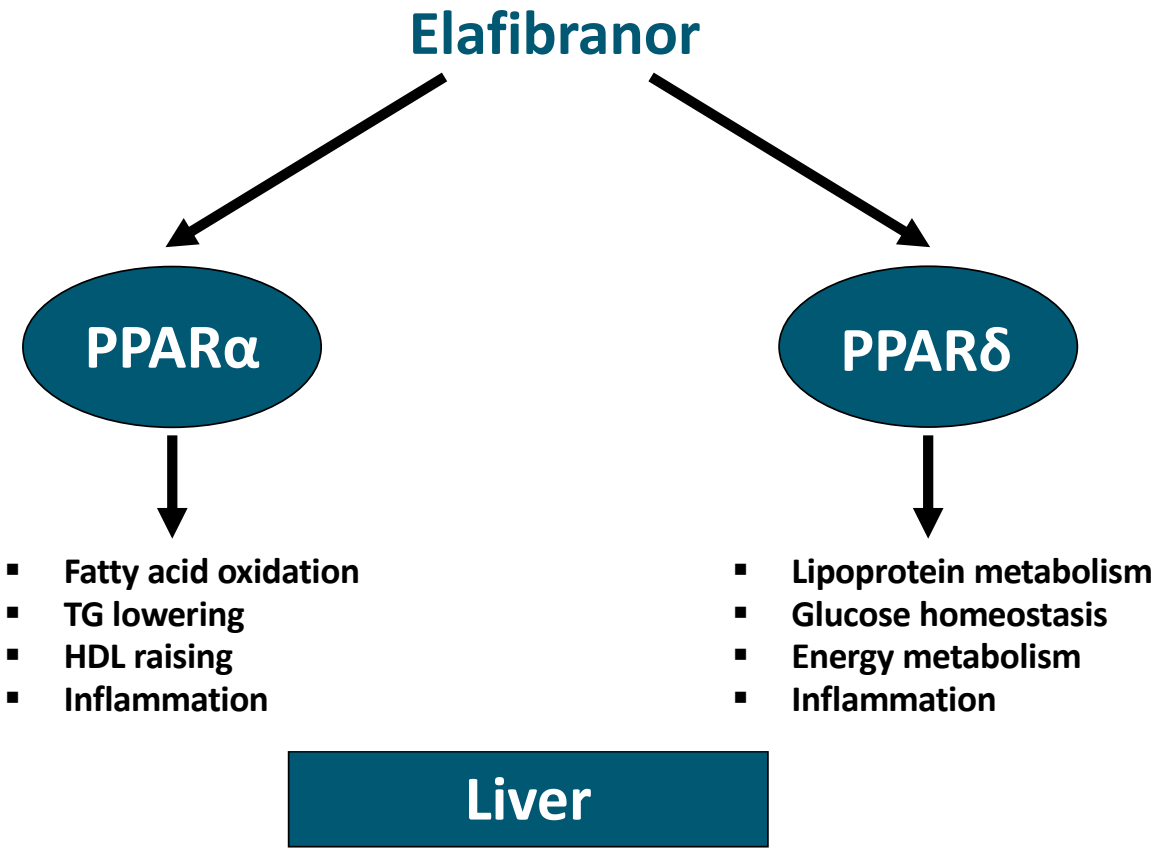
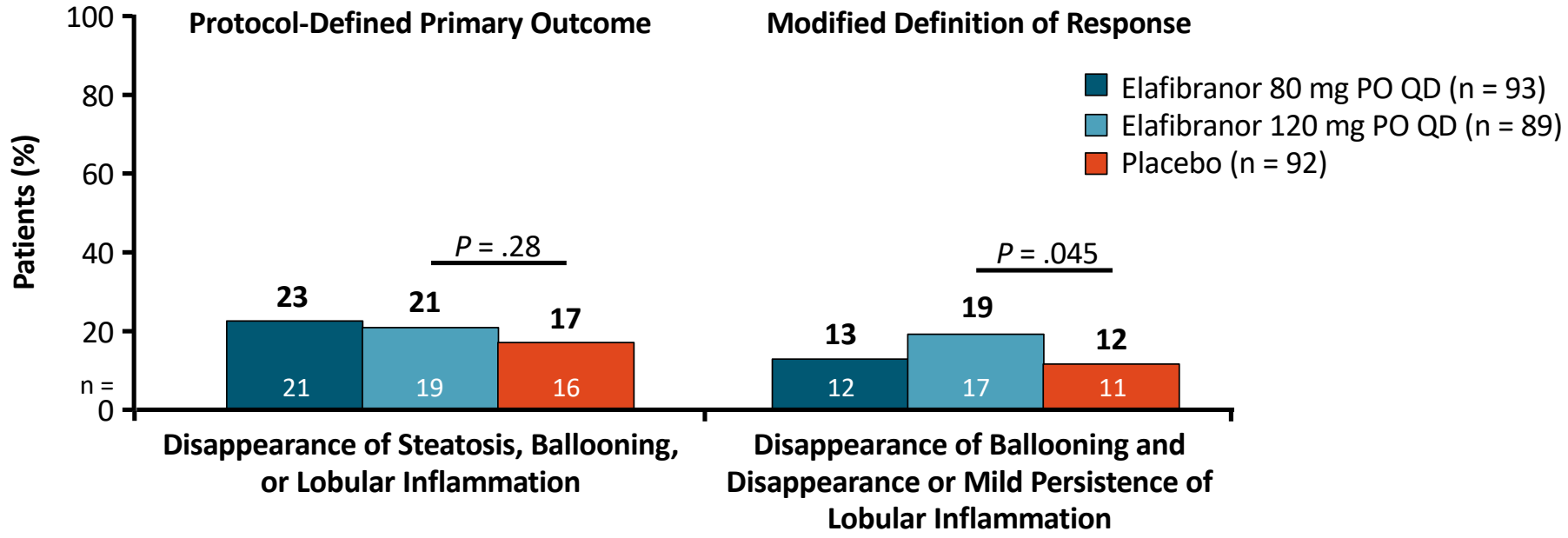
Elafibranor: PPARα/δ Agonist



Slide courtesy of Bart Staels, MD

GOLDEN-505: Elafibranor vs Placebo in Patients With NASH at Wk 52

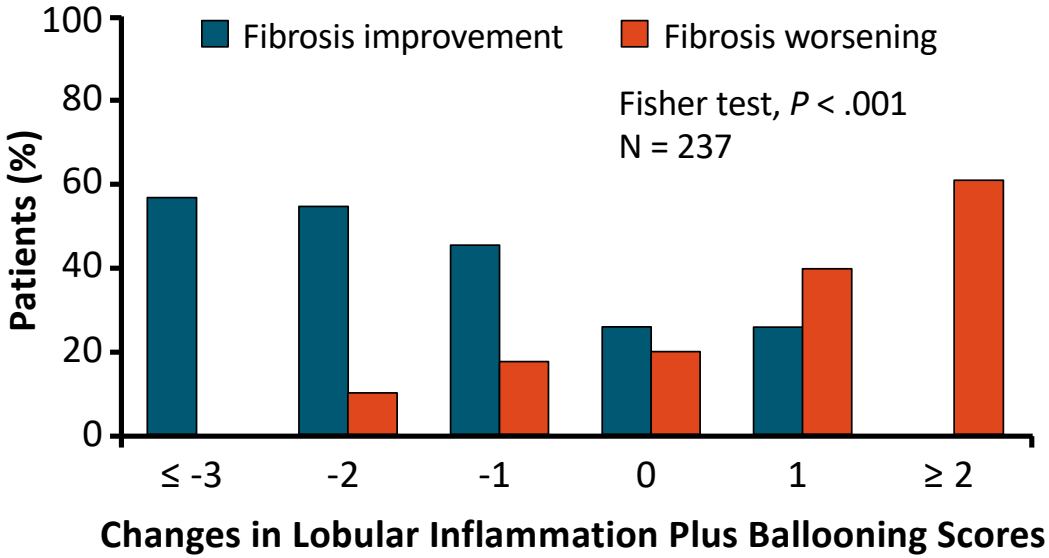
- Double-blind, placebo-controlled, randomized, international phase IIb study in patients with noncirrhotic NASH (N = 276)
  - Primary endpoint: resolution of NASH without fibrosis worsening at Wk 52



Ratziu. Gastroenterology. 2016;150:1147.

GOLDEN-505: Correlation Between NASH Histology and Fibrosis at Wk 52, Tolerability

- Changes in hepatocyte ballooning and lobular inflammation correlated with changes in fibrosis stage ($P = .04$ and $P < .001$, respectively)[1]
  - Changes in steatosis did not correlate with changes in fibrosis stage



- Liver enzymes, lipids, glucose profiles, and markers of systemic inflammation significantly lower in elafibranor 120-mg group vs the placebo group[2]
- Elafibranor well tolerated; no weight gain or cardiac events[2]
- Mild, reversible increase in serum creatinine (effect size vs placebo: increase of 4.31 ± 1.19 mmol/L; $P < .001$)[2]

1. Ratziu. AASLD 2016. Abstr LB-37. 2. Ratziu. Gastroenterology. 2016;150:1147.

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Obeticholic Acid

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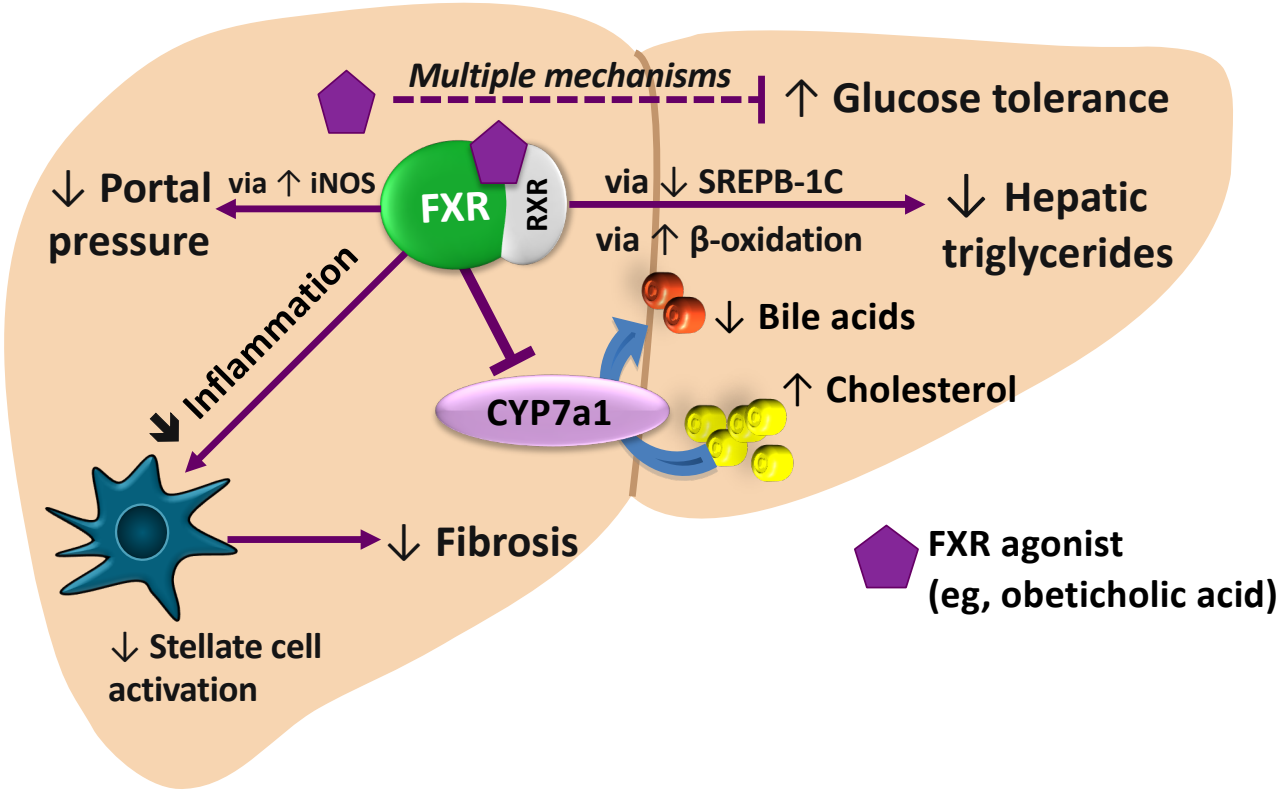
Obeticholic Acid: FXR Agonist

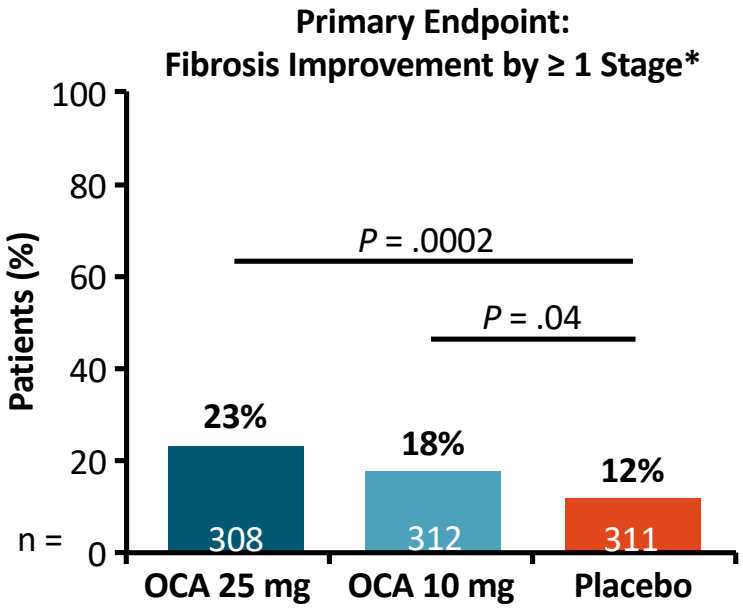
- FXR central to multiple key pathways in animal models

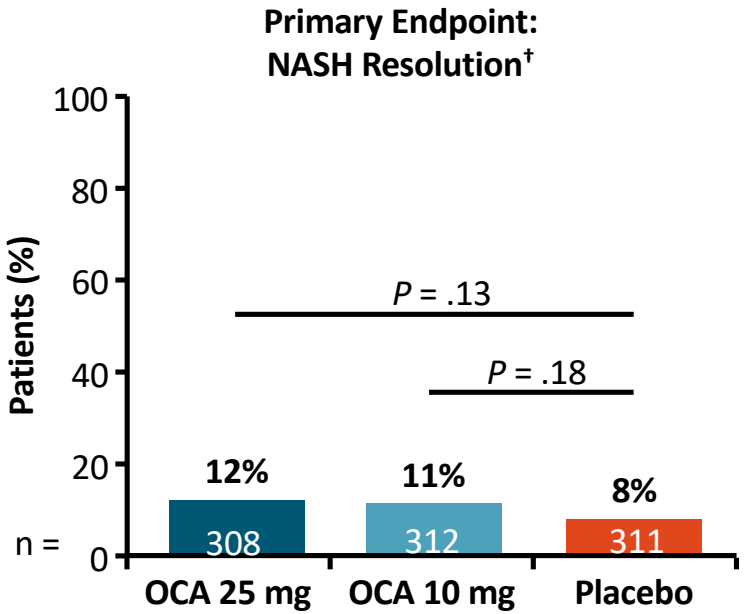


1. Cariou. Diabetes Metab. 2008;34:685. 2. Calkin. Nat Rev Mol Cell Biol. 2012;13:213. 3. Verbeke. Hepatology. 2014;59:2286.

REGENERATE: Mo 18 Efficacy of Obeticholic Acid for Treatment of NASH (ITT Population)

- Randomized, placebo-controlled phase III trial in patients with biopsy-confirmed NASH with fibrosis stage 2-3 (N = 931)





*With no worsening of NASH. †With no worsening of fibrosis.

Younossi. Lancet. 2019;394:2184.

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REGENERATE: Select AEs in Safety Population

Events, n (%)	Obeticholic Acid 10 mg (n = 653)	Obeticholic Acid 25 mg (n = 658)	Placebo (n = 657)
≥ 1 TEAE	579 (89)	601 (91)	548 (83)
▪ Leading to d/c	39 (6)	83 (13)	41 (6)
Serious AEs	72 (11)	93 (14)	75 (11)
AEs in ≥ 5% in either OCA group			
▪ Pruritis	183 (28)	336 (51)	123 (19)
▪ Nausea	72 (11)	83 (13)	77 (12)
▪ Abdominal pain	66 (10)	67 (10)	62 (9)
▪ Diarrhea	44 (7)	49 (7)	79 (12)
▪ Vomiting	34 (5)	44 (7)	33 (5)
▪ Urinary tract infection	54 (8)	62 (9)	49 (7)
▪ Upper respiratory tract infection	47 (7)	54 (8)	44 (7)
▪ Elevated LDL	109 (17)	115 (17)	47 (7)
▪ Arthralgia/Back pain	50 (8)/56 (9)	50 (8)/40 (6)	55 (8)/50 (8)
▪ Fatigue	78 (12)	71 (11)	88 (13)
▪ Headache/Dizziness	42 (6)/32 (5)	34 (5)/25 (4)	51 (8)/28 (4)

Younossi. Lancet. 2019;394:2184.

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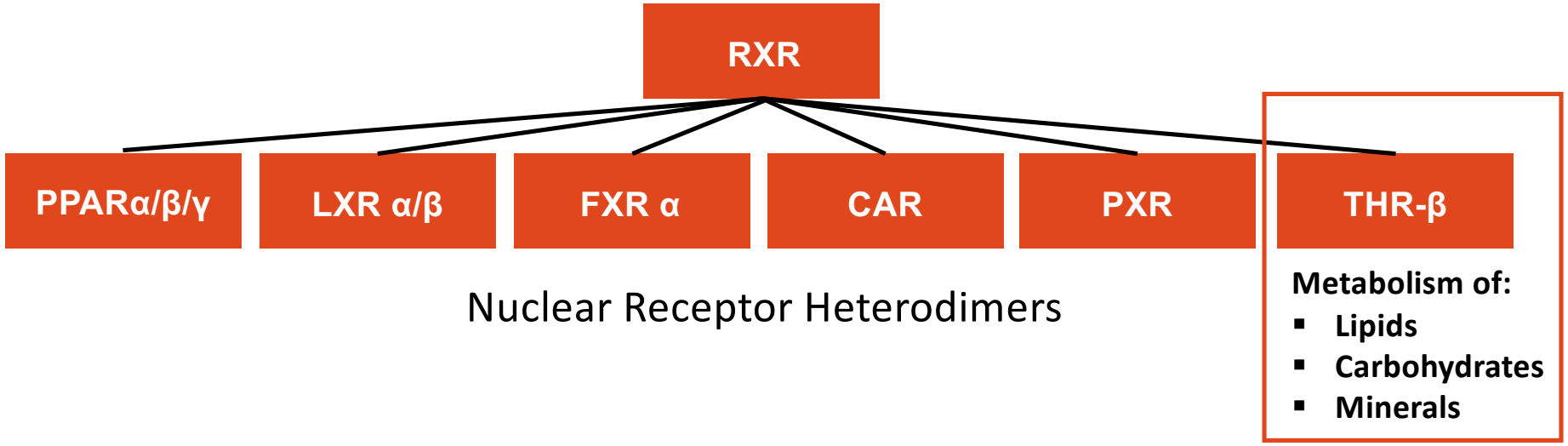
Resmetirom

Resmetirom: THR-β agonist

- Ligand-dependent transcription factors that regulate glucose and lipid metabolism in the liver
- NR1 subfamily of particular importance in NAFLD

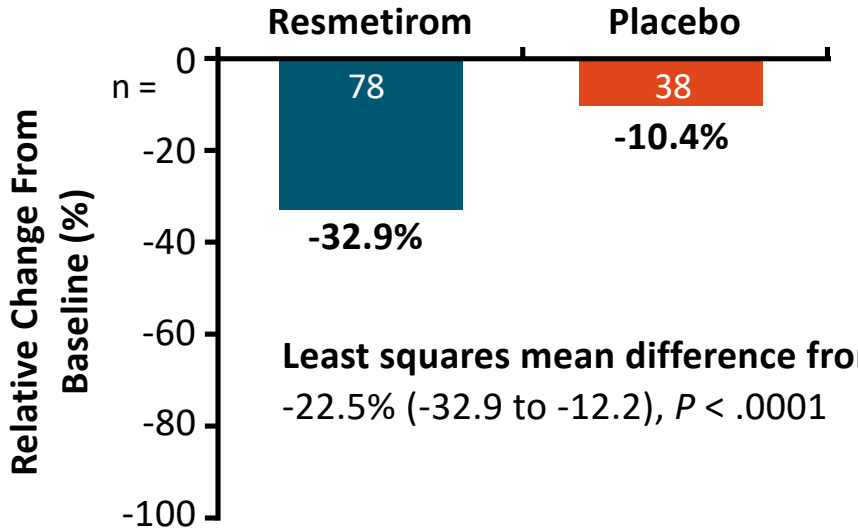


Caligiuri A, et al. Int J Mol Sci. 2016;17:1575. Younossi. Gastroenterol Hepatol (N Y). 2019;15:317. Kowalik. Front Endocrinol (Lausanne). 2018;9:382.

Resmetirom: Wk 12 Efficacy for Treatment of NASH (ITT Population)

- Randomized double-blind, placebo-controlled phase II trial in patients with biopsy-confirmed NASH with hepatic fat fraction ≥ 10%

Primary Endpoint:
Relative Change in Hepatic Fat Fraction Assessed by MRI-PDFF



Harrison. Lancet. 2019 [Epub].

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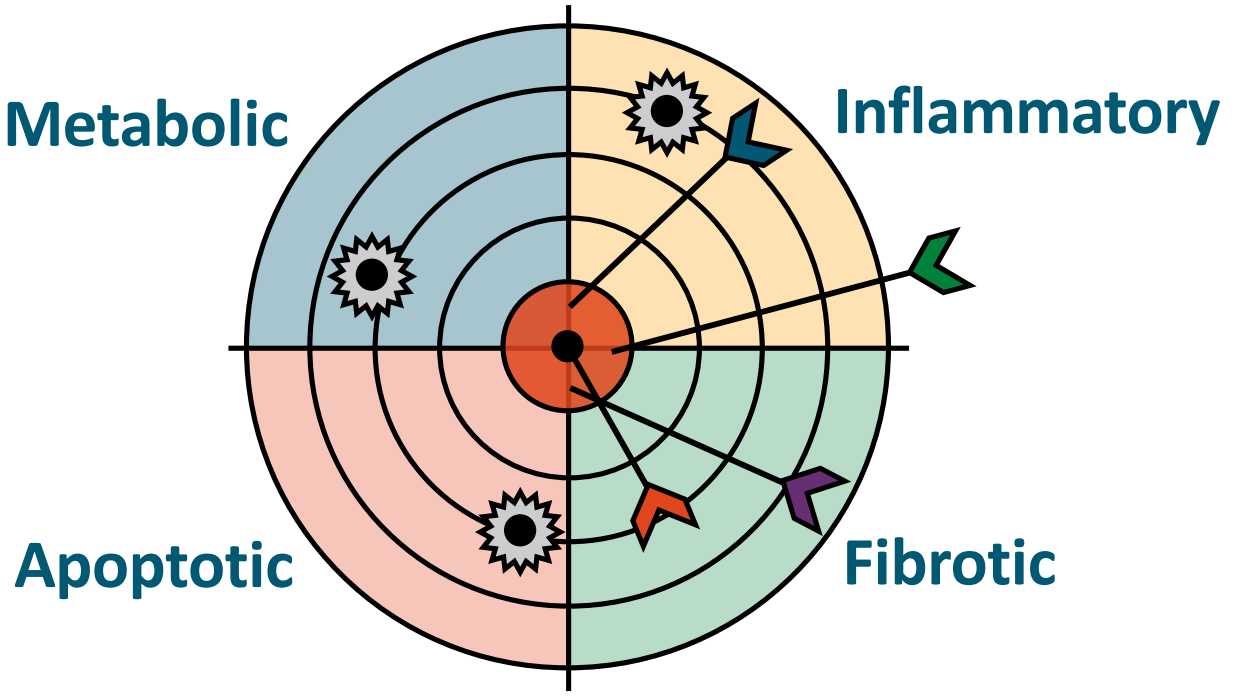
Uncertainty About Best Targets for NASH



Neuschwander-Tetri. Nat Rev Gastroenterol Hepatol. 2014;11:274.