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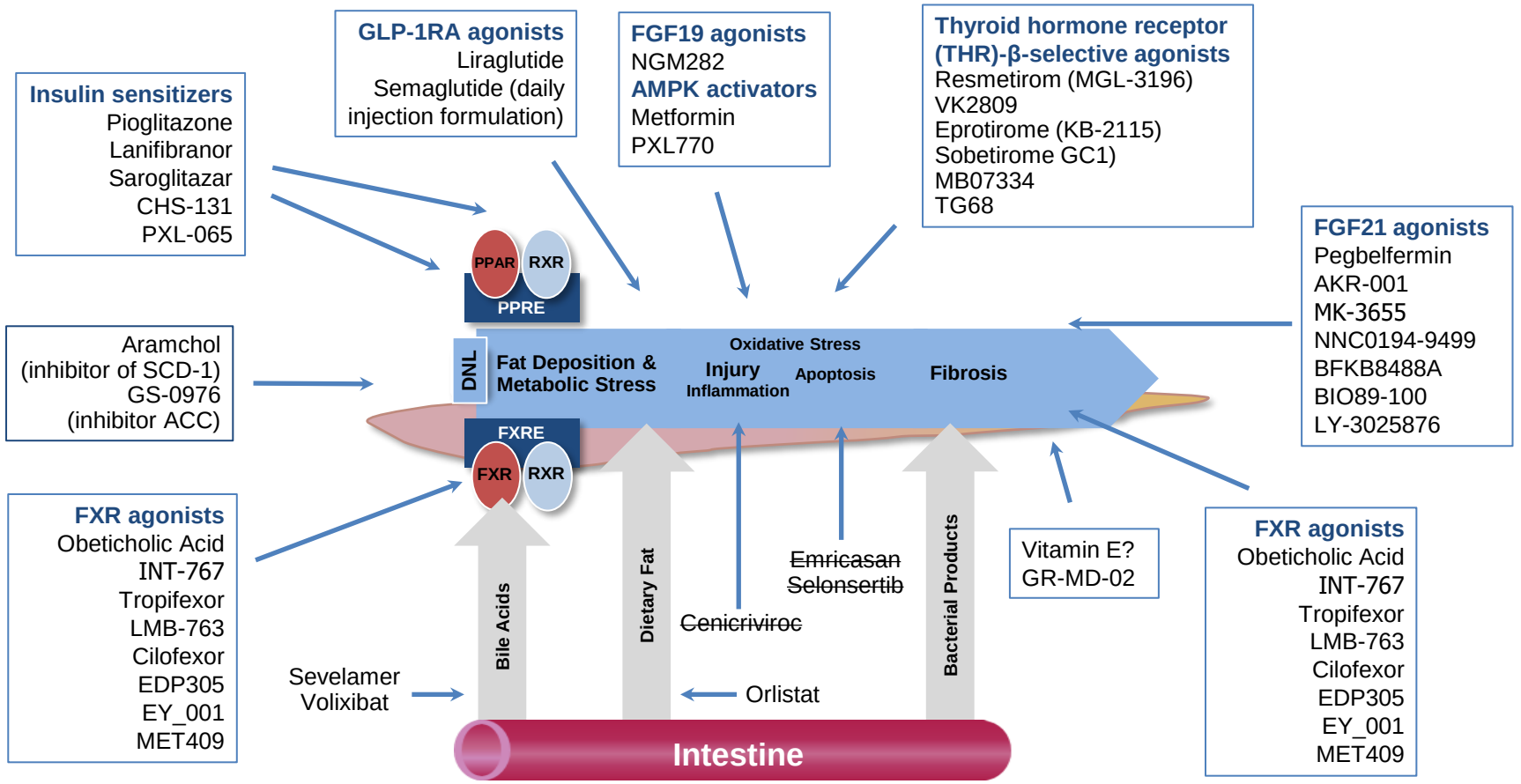
Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

New Targets and Treatments for NASH

Kenneth Cusi, MD, FACP, FACE,
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida,
Gainesville, United States

Potential Therapeutic Targets in NASH



ACC, acetyl-CoA carboxylase; DNL, *de novo* lipogenesis; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; ; GLP-1RA, glucagon-like peptide-1 receptor agonist; MPC' mitochondrial pyruvate carrier; NASH, non-alcoholic steatohepatitis; PPAR' peroxisome proliferator-activated receptor; RXR, retinoid X receptor.

Adapted from Rotman et al. *Gut.* 2017;66:180–90

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

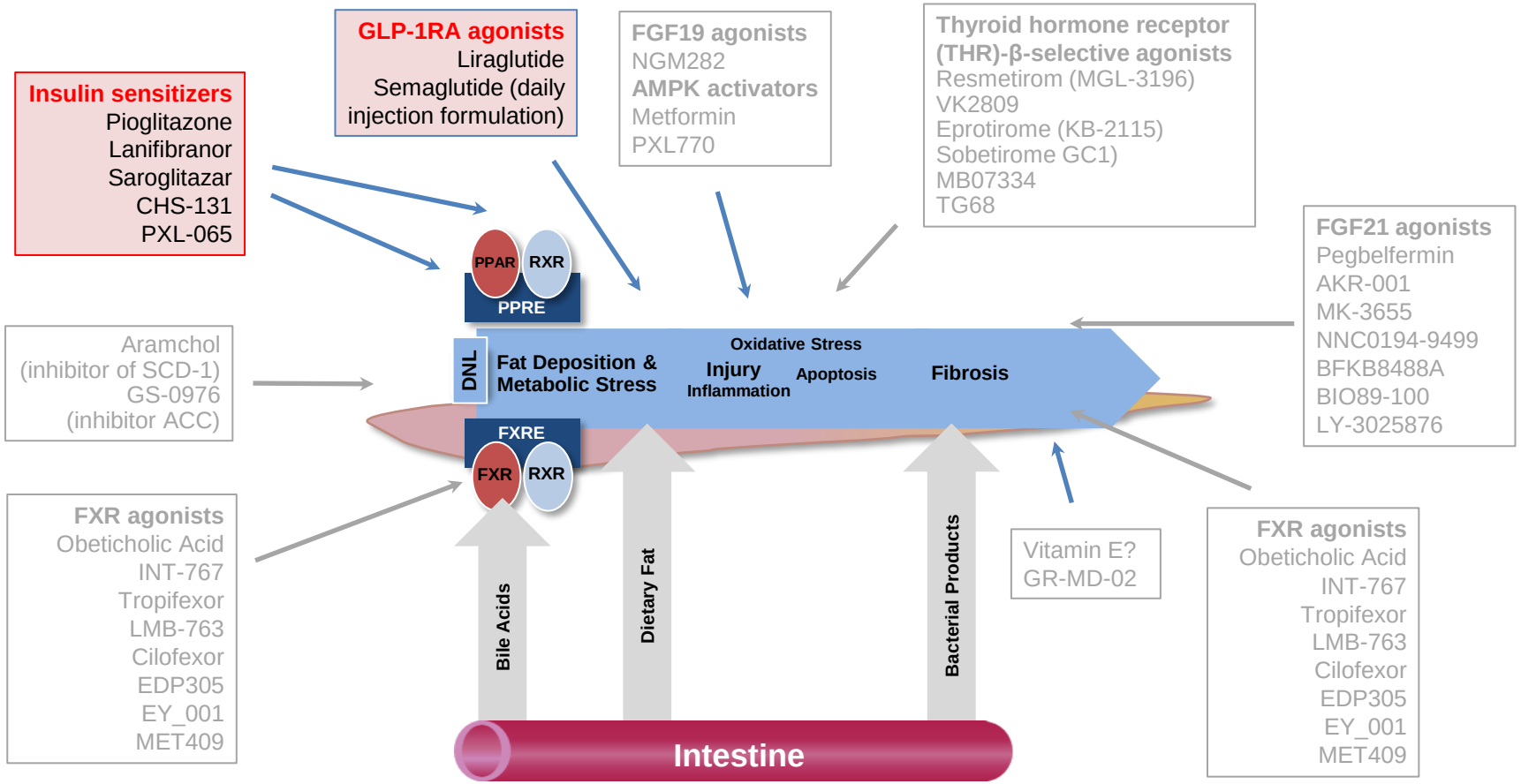
and

- No worsening of steatohepatitis

- NASH and fibrosis must be evaluated independently, as treatment may have different effects on each

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 Draft Guidance.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

Potential Therapeutic Targets in NASH



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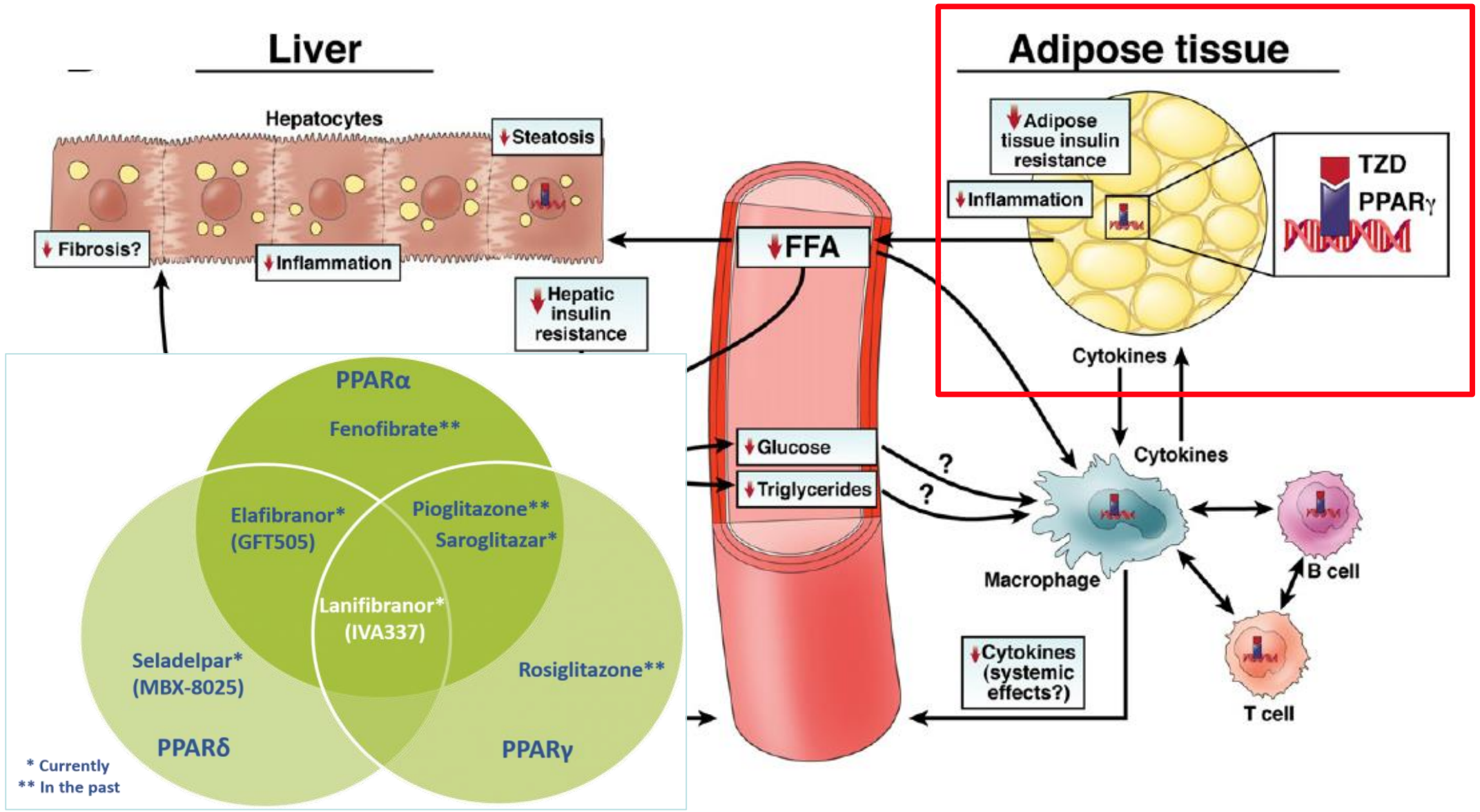
Adapted from Rotman et al. Gut. 2017;66:180–90

Rationale for PPARs in NASH



Cusi K. Gastroenterology 2012, 142:711-25

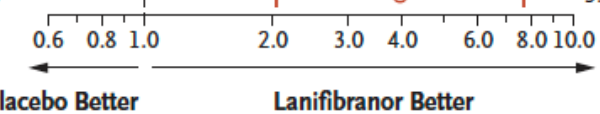
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2021 VOL. 385 NO. 17

A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

S.M. Francque, P. Bedossa, V. Ratziu, Q.M. Anstee, E. Bugianesi, A.J. Sanyal, R. Loomba, S.A. Harrison, R. Balabanska, L. Mateva, N. Lanthier, N. Alkhouri, C. Moreno, J.M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M.-P. Richard, J.-L. Abitbol, P. Broqua, J.-L. Junien, and M.F. Abdelmalek, for the NATIVE Study Group*

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	



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Novel GLP-1RAs for NASH

Kenneth Cusi, MD, FACP, FACE,
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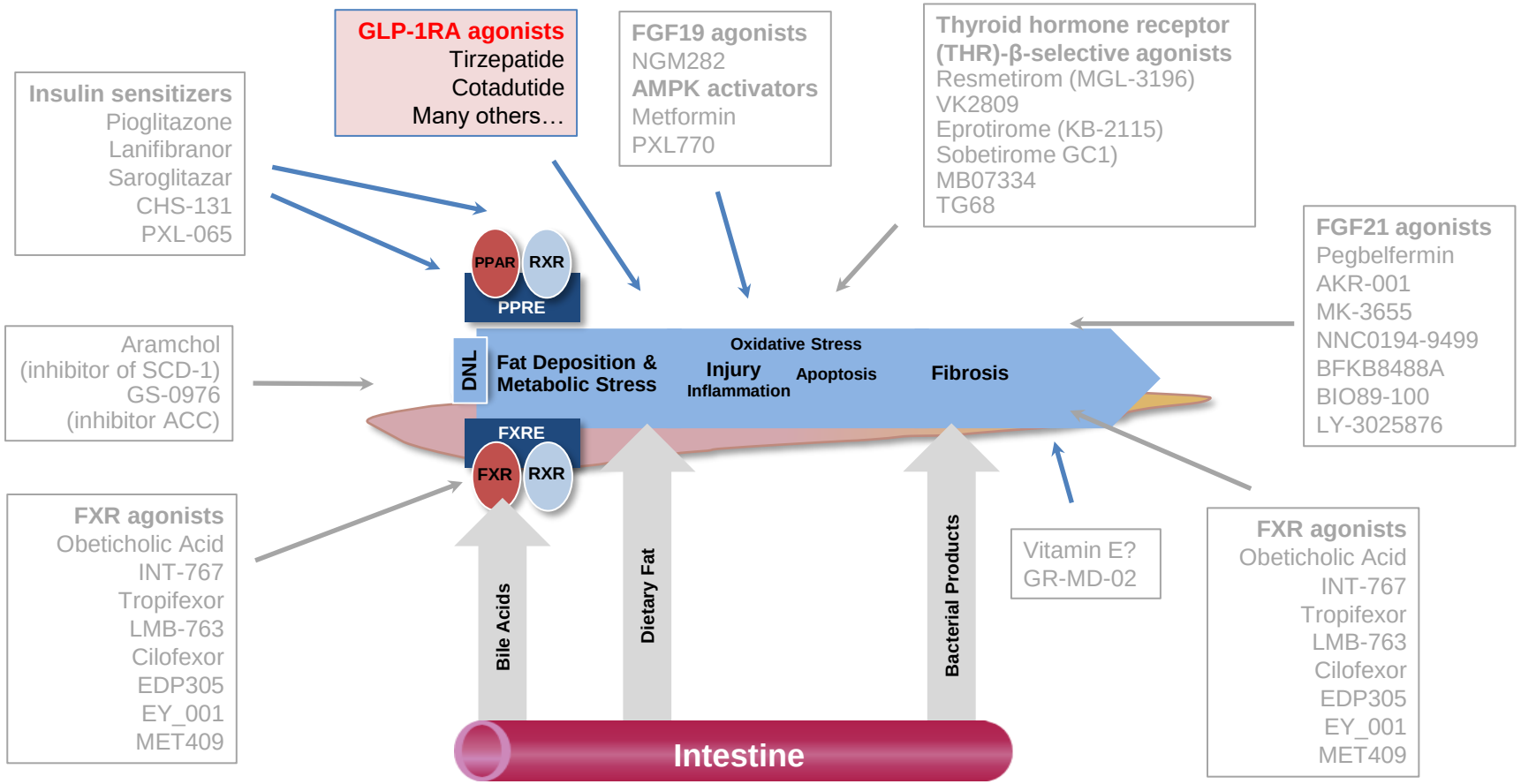
Potential Therapeutic Targets in NASH



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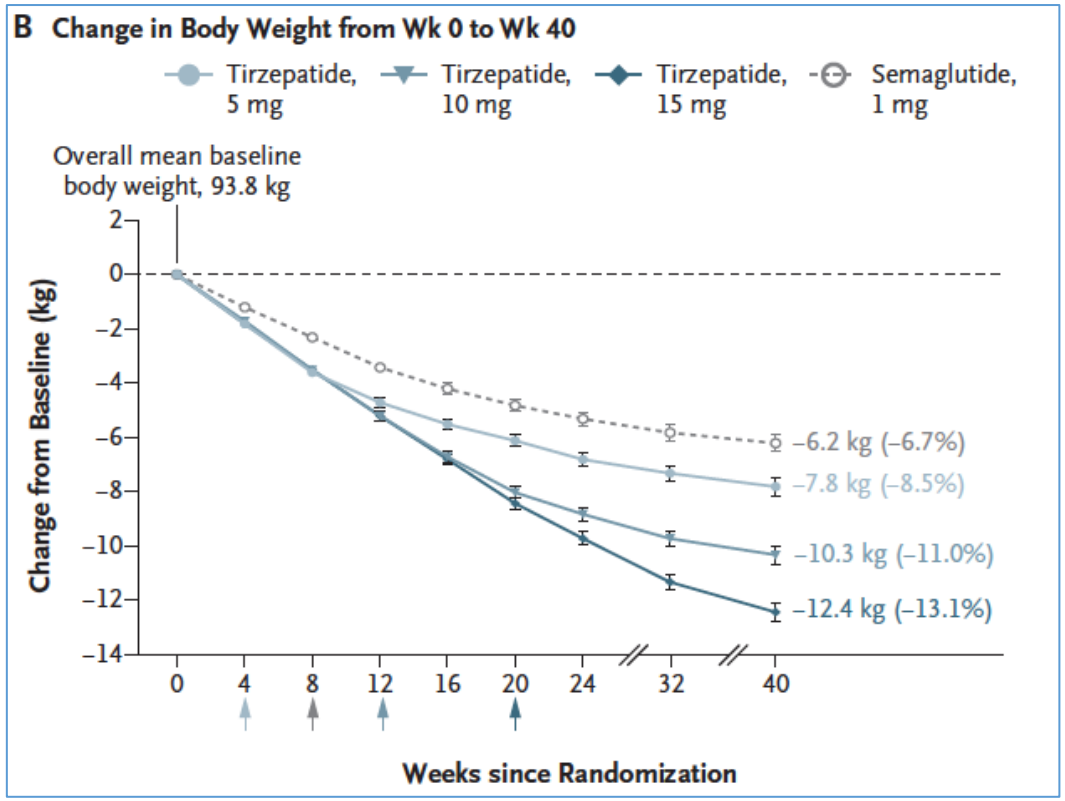
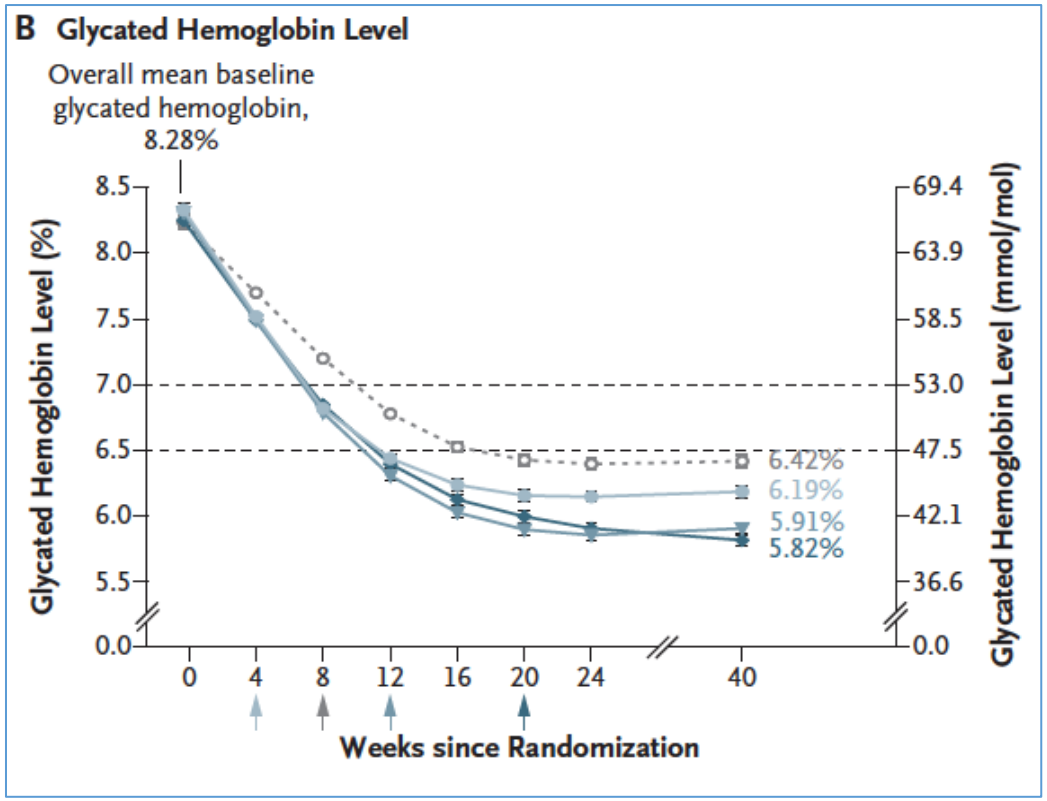
Adapted from Rotman et al. Gut. 2017;66:180–90

Tirzepatide versus Semaglutide Once weekly in Patients with Type 2 Diabetes

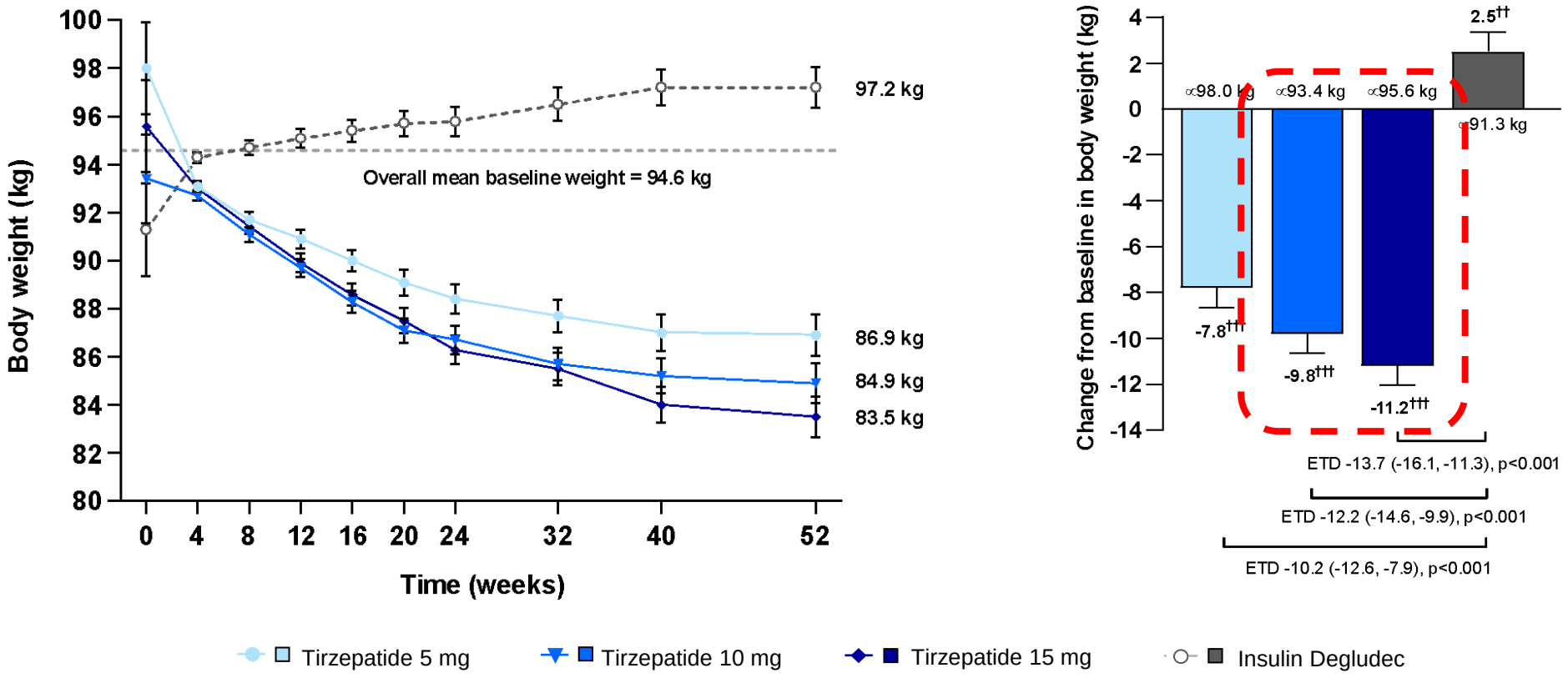




Frías, Juan P., et al. New England Journal of Medicine 385.6 (2021): 503-515.

SURPASS-3: Tirzepatide vs. Basal Insulin

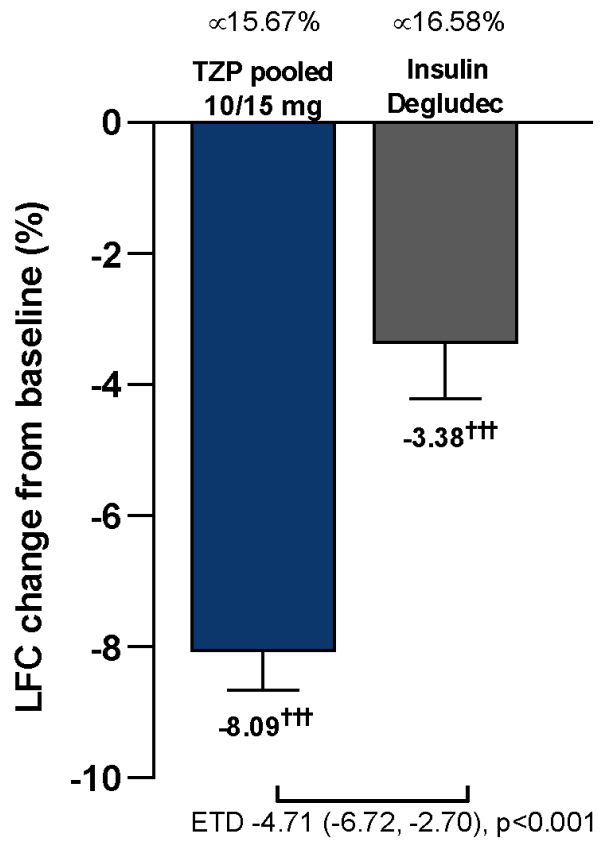
Change from Baseline in Weight after 52 Weeks of Treatment

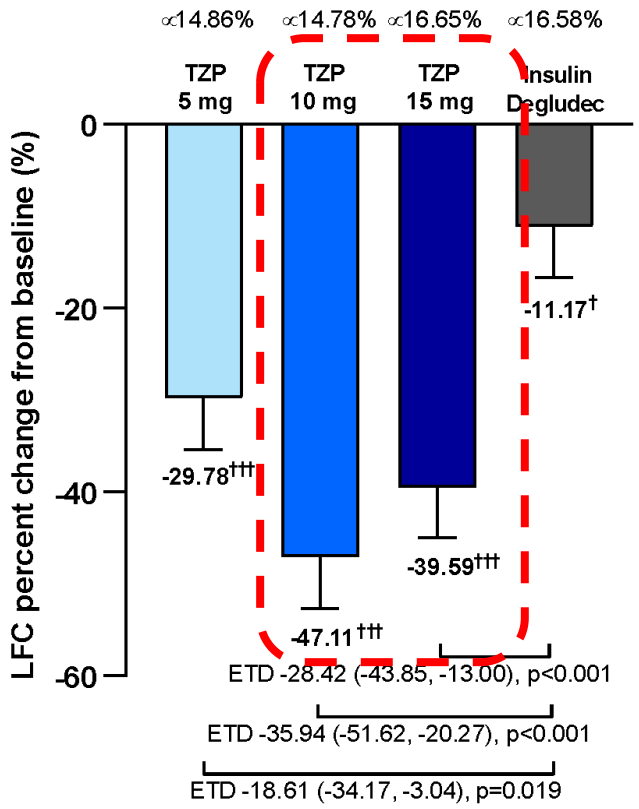


Data are LSM (SE) over time and at 52 weeks. Estimated treatment differences (ETD) at 52 weeks are LSM (95% CI); mITT (efficacy analysis set). MMRM analysis. †† p<0.01; ††† p<0.001 vs. baseline within treatment group. ∝ represents the mean value at baseline for the respective group.

SURPASS-3: Tirzepatide vs. Basal Insulin

Change from Baseline in Liver Fat Content after 52 Weeks of Treatment





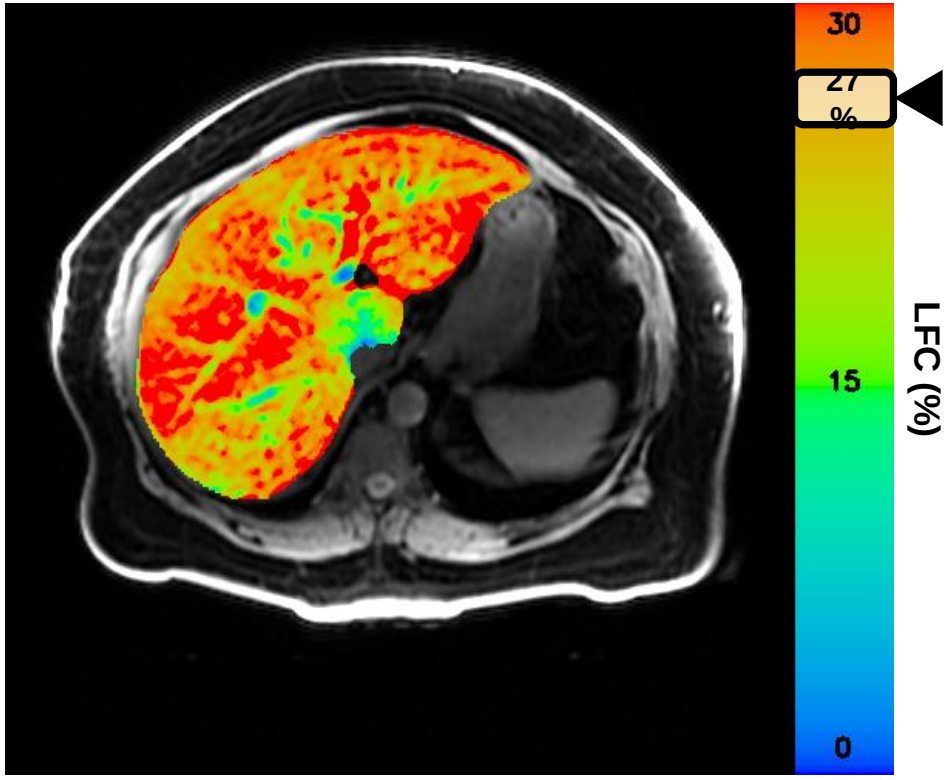
Data are LSM (SE) at 52 weeks. Estimated treatment differences (ETD) at 52 weeks are LSM (95% CI); mITT (MRI analysis set). ANCOVA analysis. † p<0.05; ††† p<0.001 vs. baseline within treatment group. ∝ represents the mean value at baseline for the respective group.

(Presented at the annual European Association for the Study of Diabetes meeting, Gastaldelli, Cusi et al, September 2021)

SURPASS-3: Tirzepatide vs. Basal Insulin

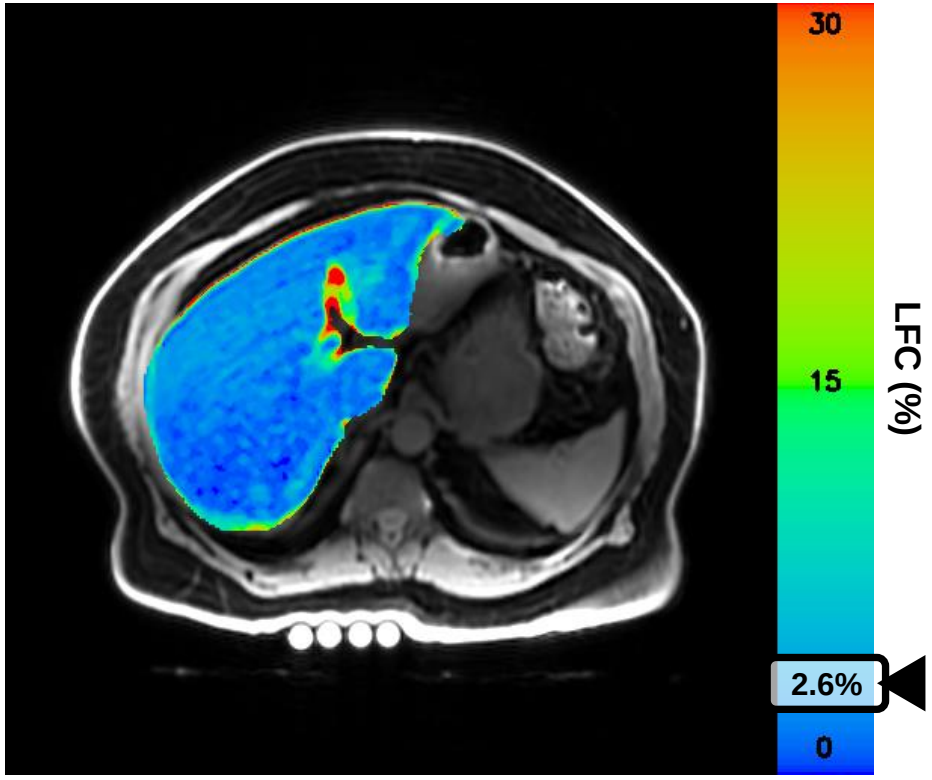
Liver Fat Content Before and After 52 weeks of Tirzepatide 5 mg/week in a 59 year old male on metformin + SGLT-2i

MRI scan at baseline



BMI: 44.8 kg/m^2; body weight: 134.2 kg
HbA_{1c}: 78.1 mmol/mol (9.3%)
FSG: 10.3 mmol/L (186 mg/dL)

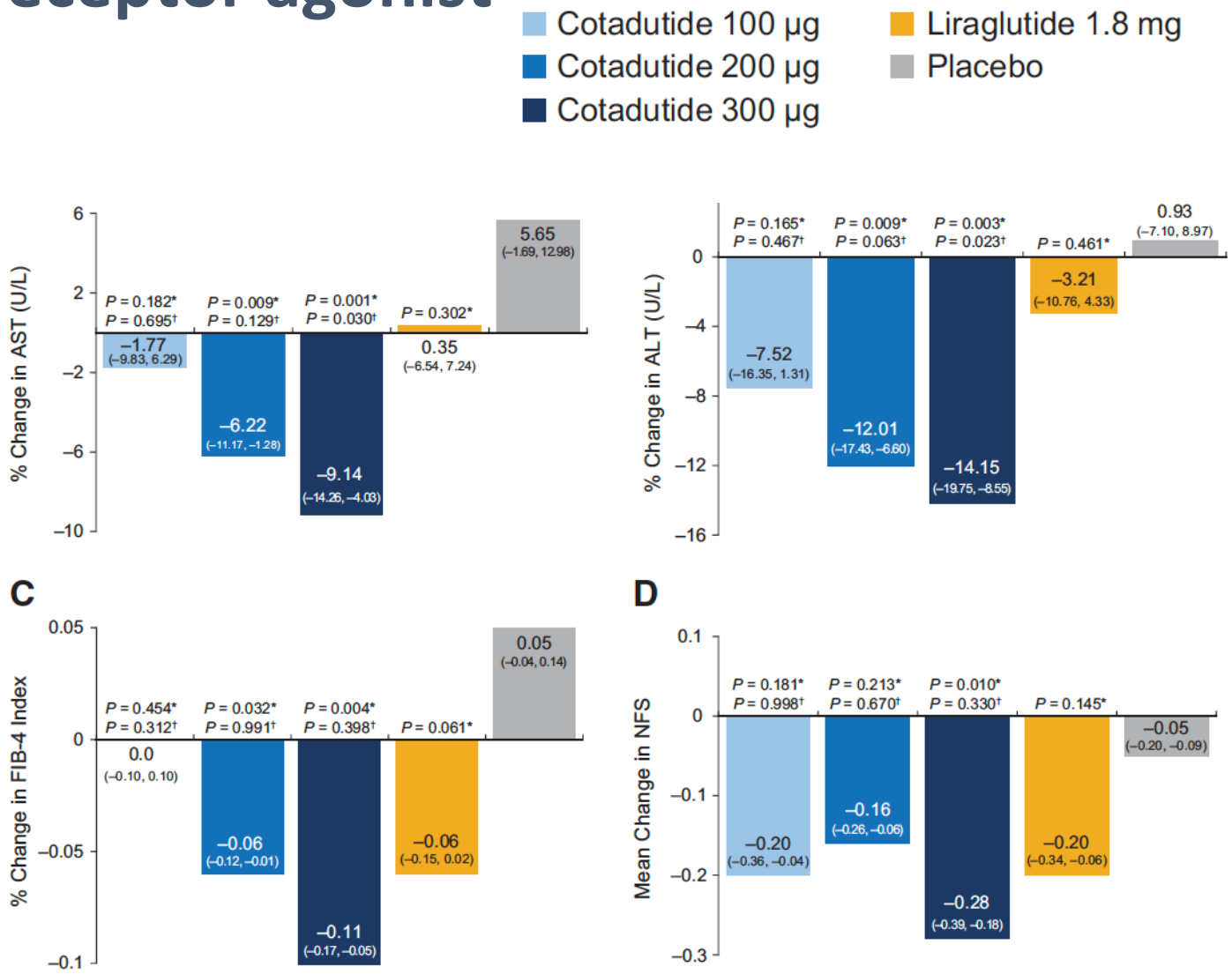
MRI scan at 52 weeks



BMI: 36.2 kg/m^2; body weight: 108.4 kg
HbA_{1c}: 43.2 mmol/mol (6.1%)
FSG: 5.9 mmol/L (107 mg/dL)

Cotadutide, a dual GLP-1 and glucagon receptor agonist

Effects of Cotadutide on Metabolic and Hepatic Parameters in Adults With Overweight or Obesity and Type 2 Diabetes: A 54-Week Randomized Phase 2b Study



Nahra, Rajaa, et al. Diabetes Care 44.6 (2021): 1433-1442.

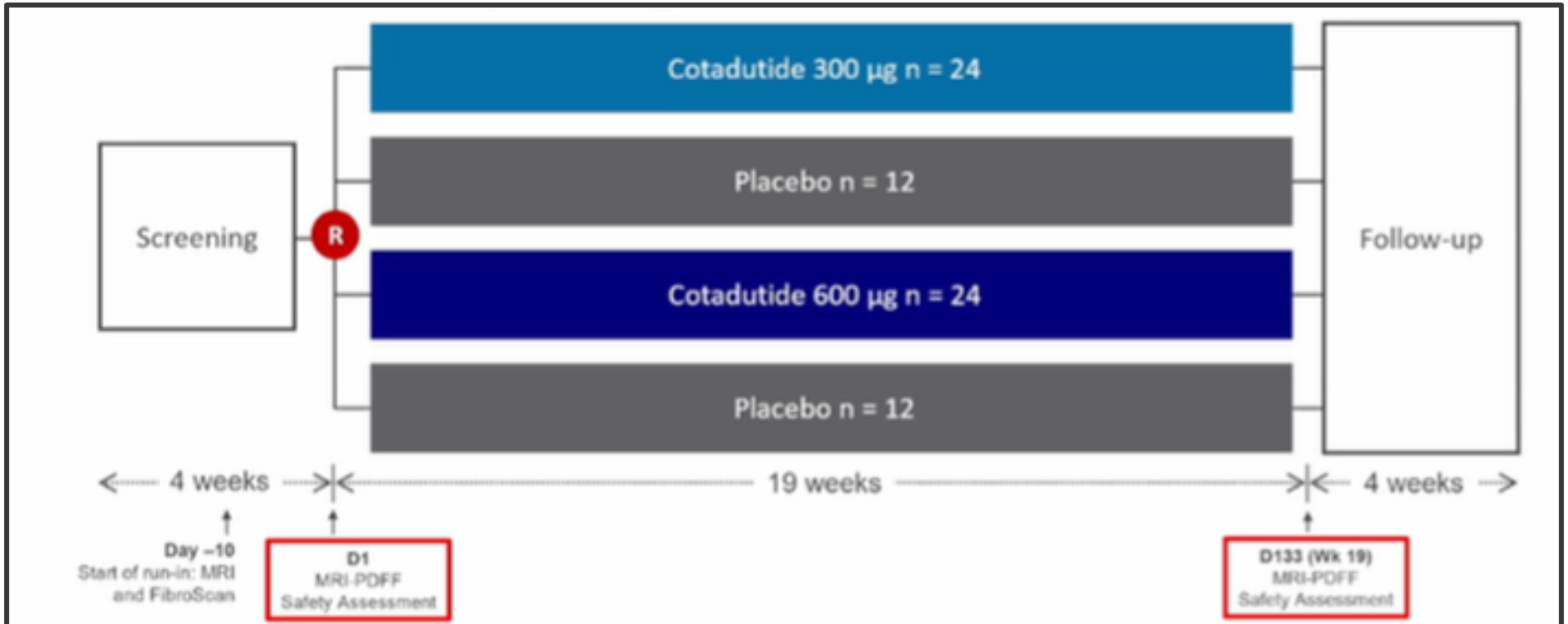
Cotadutide, a dual GLP-1 and glucagon receptor agonist

PROXYMO DEMONSTRATES SAFETY AND EFFICACY OF COTADUTIDE, A NOVEL INCRETIN CO-AGONIST IN BIOPSY-PROVEN NON-CIRRHOTIC NASH WITH FIBROSIS

Darren Robertson, Benjamin Challis, Samuel J Daniels, Janeli Sarv, José Sánchez, Jennifer Schumi, Antonio Manzur, Li-Ming Gan, Lutz Jermutus, **Arun J Sanyal** and Sudha S Shankar

The Liver Meeting, AASLD, 12 –15 Nov 2021, LO6

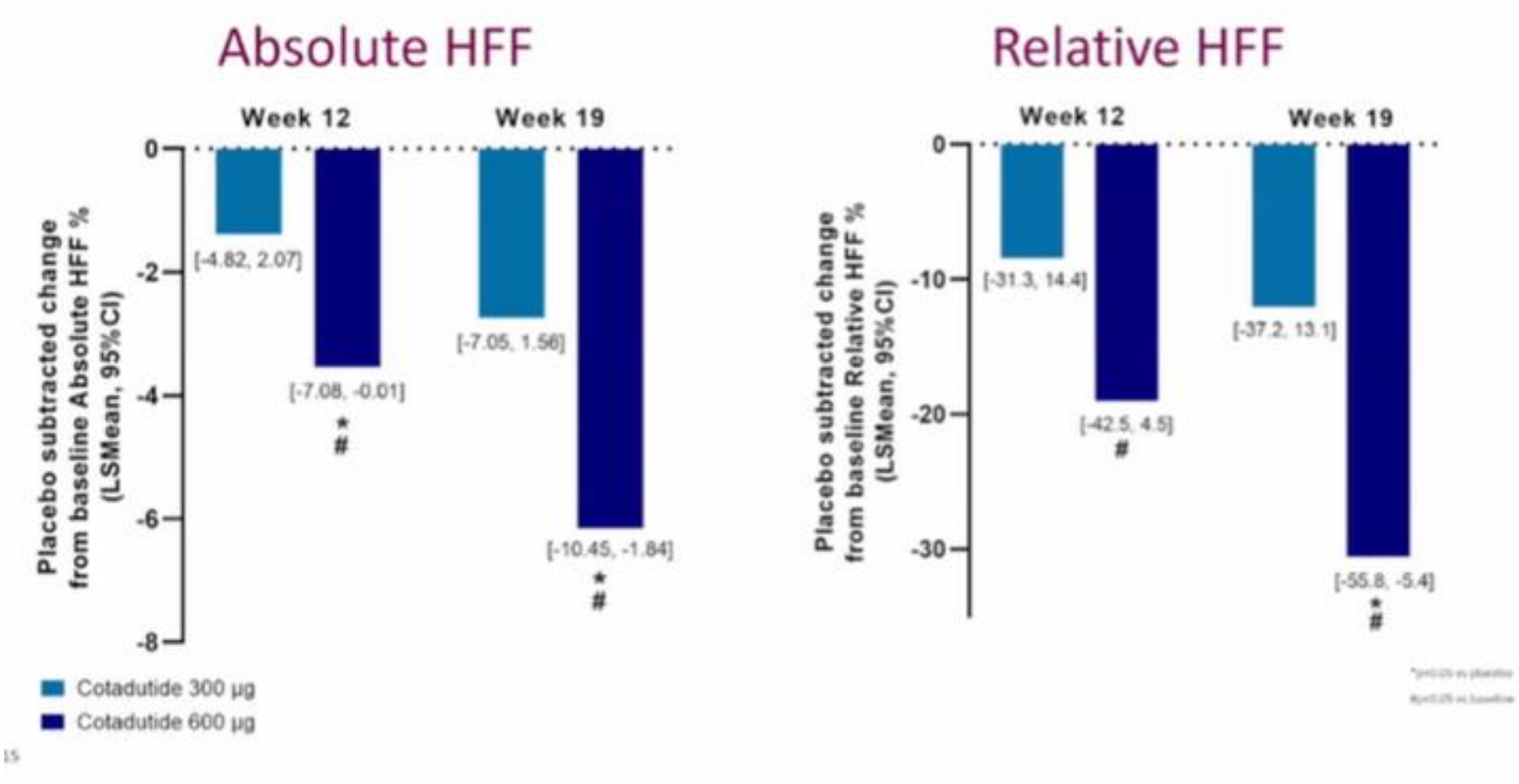
PROXYMO Study Design



Population:

- Adults with biopsy-proven non-cirrhotic NASH with fibrosis (NAS ≥ 4, fibrosis stages F1–3 per NASH CRN criteria)
- Hepatic steatosis ≥ 10% by MRI-PDFF at screening
- BMI ≥ 30 kg/m^2
- T2DM: HbA1c < 9.5% on stable oral anti-diabetic therapy

Effect of Cotadutide on Hepatic Steatosis



Overall Adverse Events

AE Category	Placebo (n = 24)	Cotadutide 300 µg (n = 26)	Cotadutide 600 µg (n = 24)	Cotadutide Overall (n = 50)
Any AE n(%)	9 (37.5)	20 (76.9)	22 (91.7)	42 (84.0)
Death	0	0	0	0
Any SAE (including death)	1 (4.2)	1 (3.8)	1 (4.2)	2 (4.0)
Any AE leading to discontinuation of IP	1 (4.2)	2 (7.7)	4 (16.7)	6 (12.0)
Any AE leading to withdrawal from study	0	0	0	0

- More AEs noted for cotadutide treated groups versus placebo as expected with this class of molecule
- No deaths and few SAEs which were balanced across treatment arms: Total of 3 SAEs were reported
- Discontinuations were higher on cotadutide and higher in the 600 µg versus the 300 µg group

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Potential role of FGF-19, FGF-21 and Thyroid Hormone receptor (THR)-β-Selective Agonists in NASH

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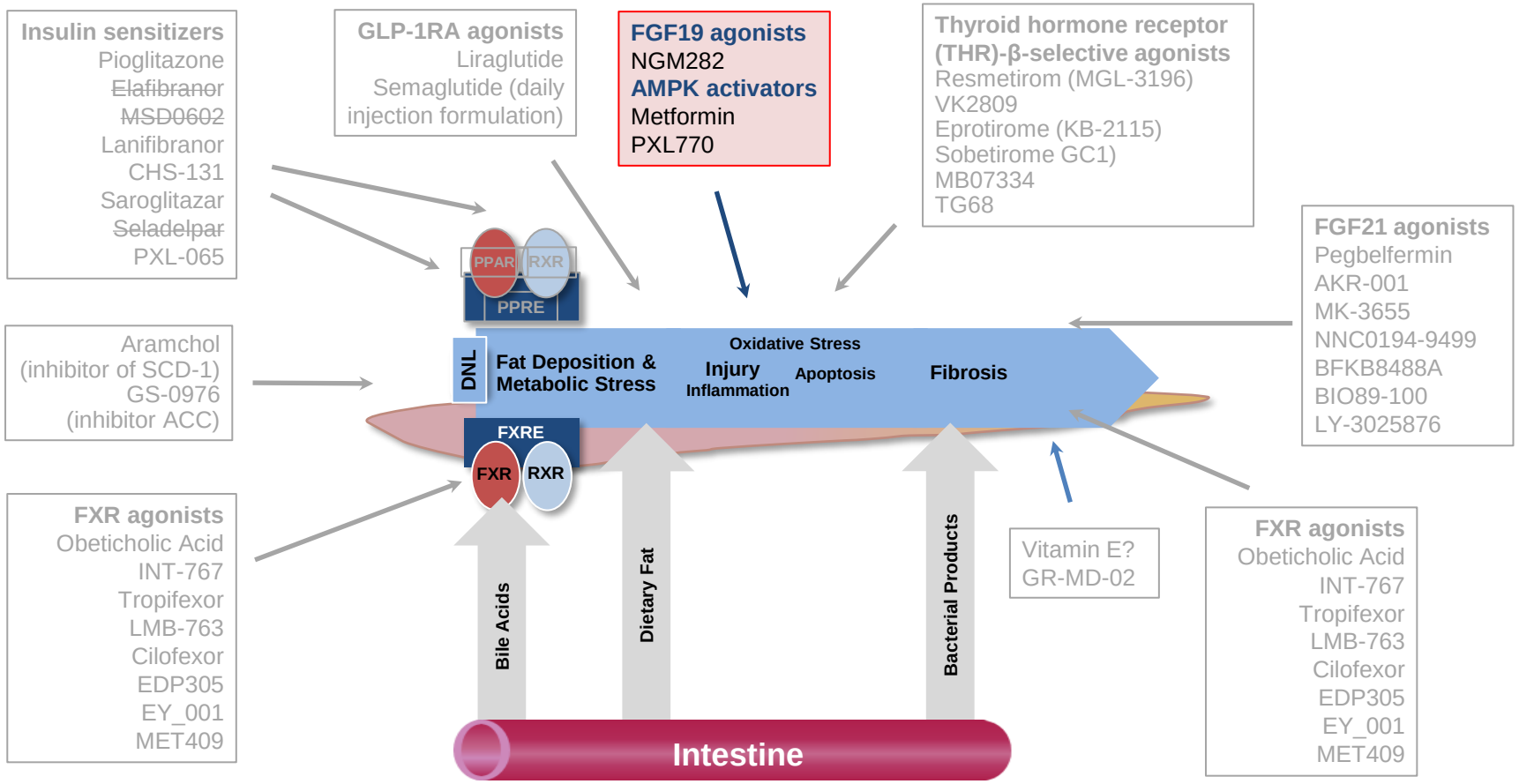
Potential Therapeutic Targets in NASH



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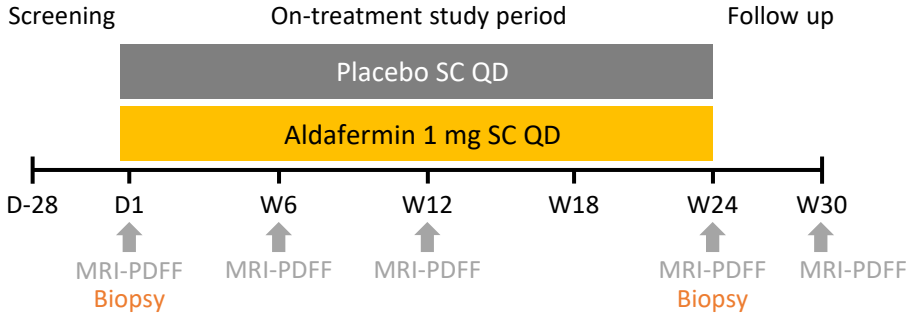
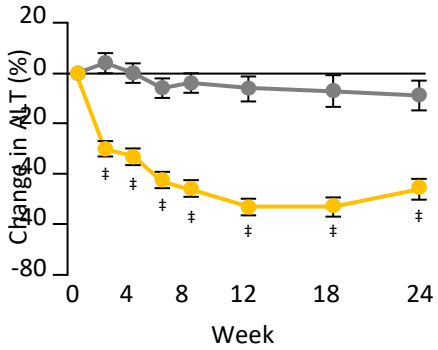
Adapted from Rotman et al. Gut. 2017;66:180–90

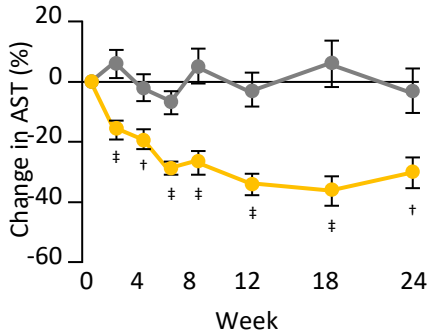
Aldafermin (NGM282; FGF-19 analog):

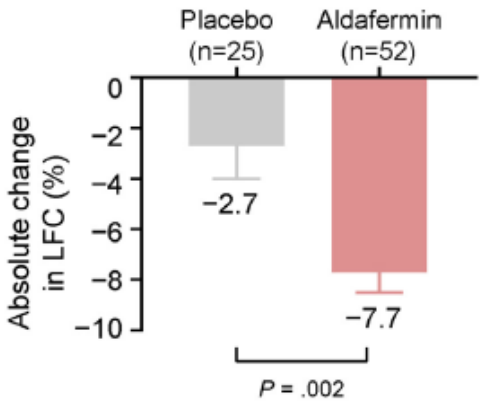
24-week RCT in patients with nonalcoholic steatohepatitis

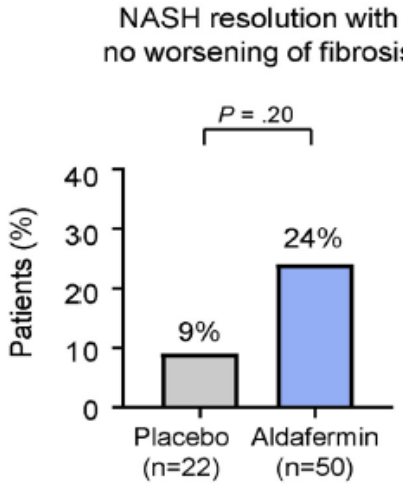


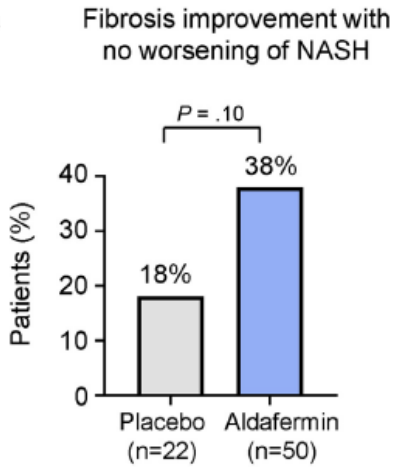
*p<0.05; †p<0.01; ‡p<0.001 vs placebo.

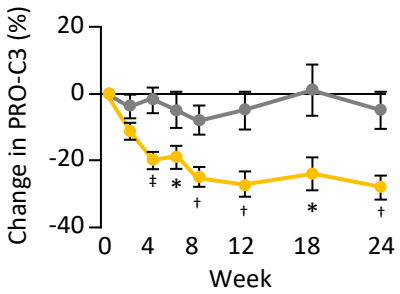








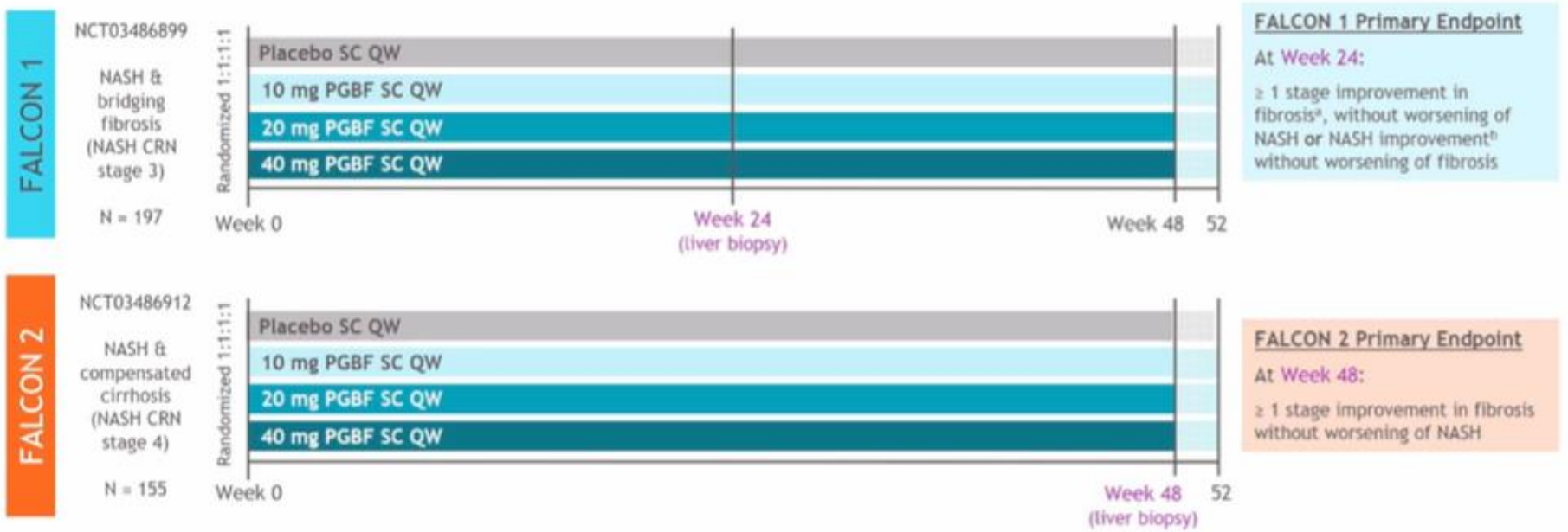




Conclusion: Aldafermin reduces liver fat content with a trend towards resolution of NASH and fibrosis improvement.

Harrison S, et al. Gastroenterology 2021

FALCON Phase 2b Program in Advanced NASH

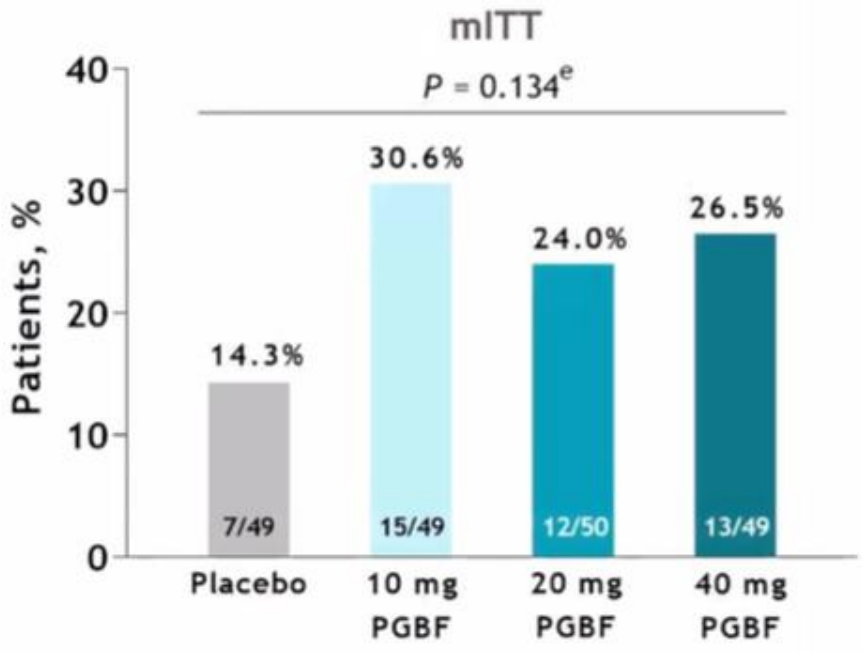


FALCON 2 primary study data are presented in poster LP8

[a]Improvement of fibrosis = ≥ 1 stage decrease in NASH CRN fibrosis score; [b]NASH improvement = ≥ 2 point decrease in NAS with contribution from > 1 NAS component.
NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; PGBF, pegbelfermin; QW, once weekly; SC, subcutaneous.

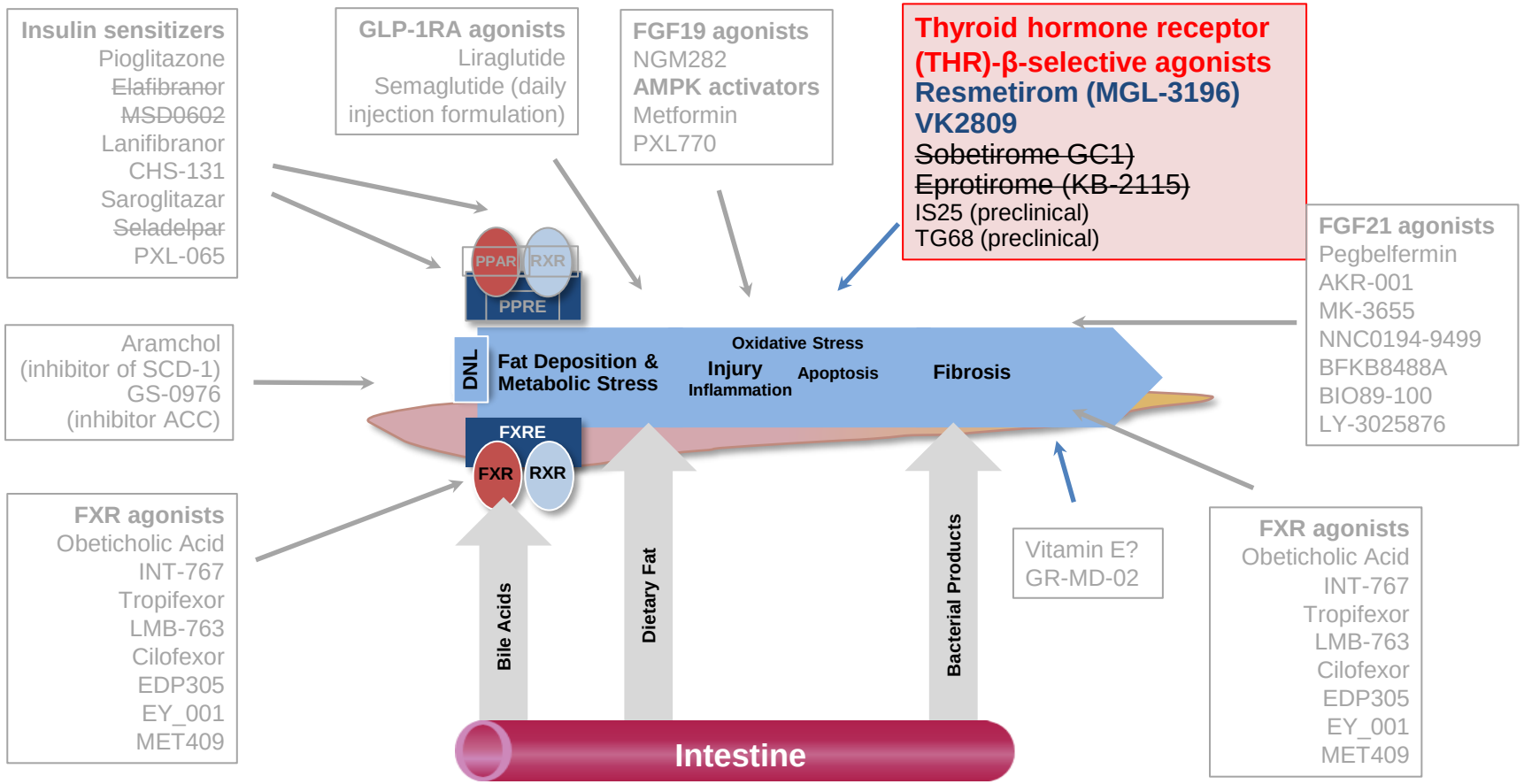
Primary Endpoint

At Week 24: ≥ 1 stage improvement in fibrosis[a] without worsening of NASH[b] OR NASH improvement[c] without worsening of fibrosis[d]



[a]Improvement of fibrosis = ≥ 1 stage decrease in NASH CRN fibrosis score; [b]Worsening of NASH = increase in NAS by ≥ 1 point; [c]NASH improvement = ≥ 2 point decrease in NAS with contribution from > 1 NAS component; [d]Worsening of fibrosis = ≥ 1 stage increase in NASH CRN fibrosis score; [e]Cochran-Armitage trend test across proportions of responders in the treatment groups at a 1-sided 0.05 level of significance provided at least 80% power if 160 patients were randomized 1:1:1:1. mITT, modified intent-to-treat; NASH, nonalcoholic steatohepatitis; PGBF, pegbelfermin.

Potential Therapeutic Targets in NASH



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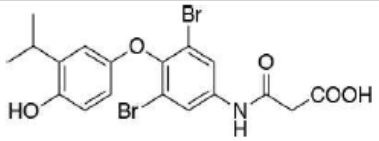
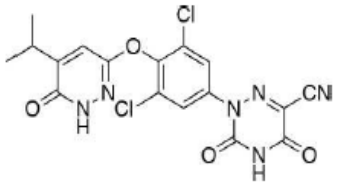
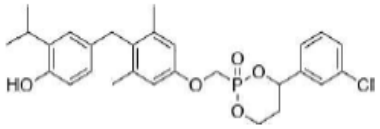
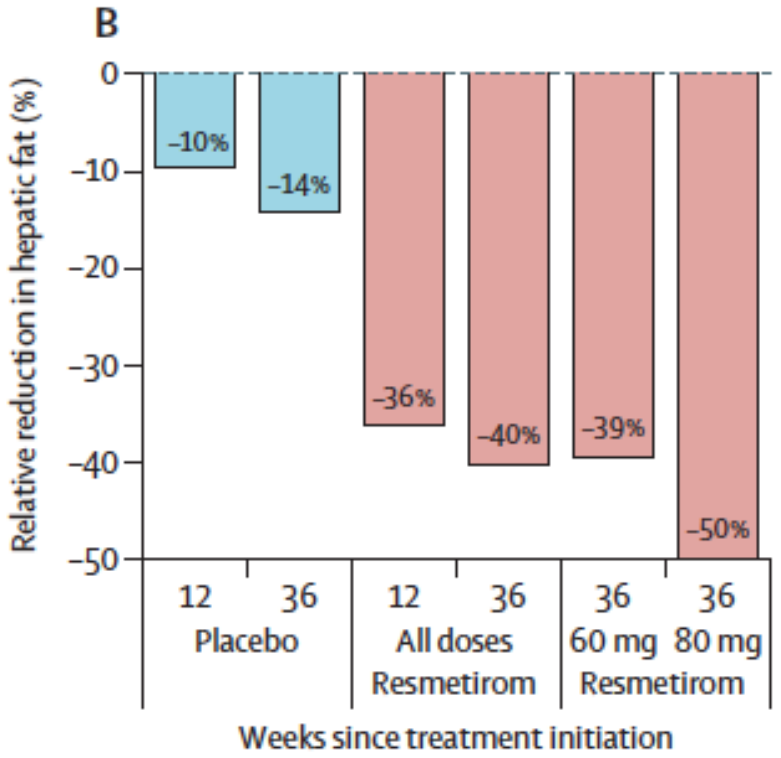
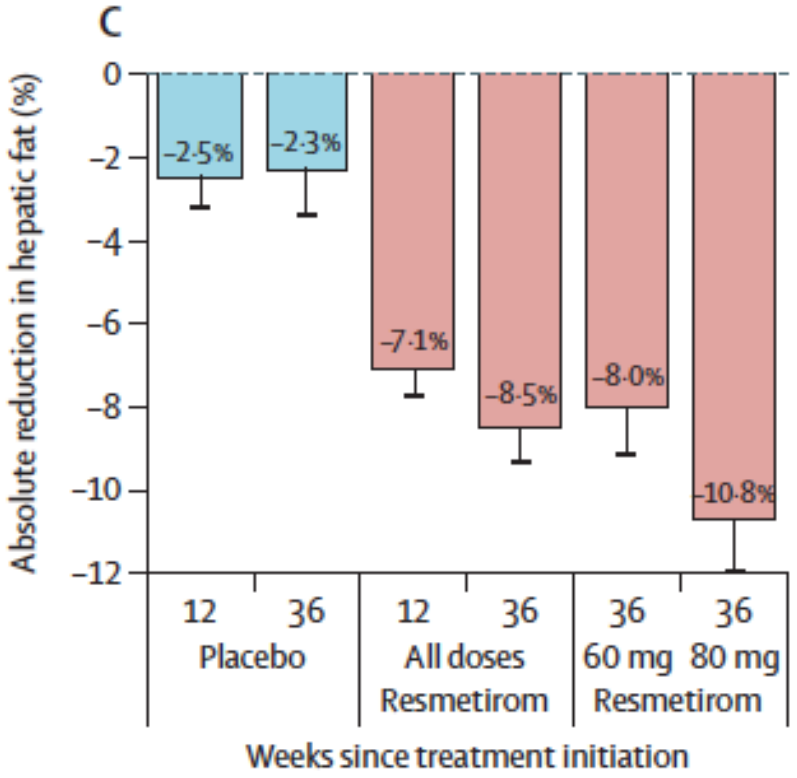
Adapted from Rotman et al. Gut. 2017;66:180–90

Thyroid hormone receptor (THR)-β-selective agonists

Eprotirome (KB2115) *KaroBio*		↓Total cholesterol ↓LDL cholesterol ↓Lp(a) ↓triglycerides [Berkenstam et al. (66); Sjouke et al. (69)]	Upregulation of LDL receptors and cardio-vascular risks Liver toxicity; increase of AST and ALT levels Cartilage Defect in Dogs Terminated during Phase 3
Resmetirom (MGL-3196) *Madrigal Pharmaceutical*		↓Hepatic fat in patients with NASH [Kelly et al. (70); Harrison et al. (71)]	No adverse side effects after Phase 2 clinical trails Phase 3 in progress (NCT03900429)
VK2809 (MB08711) *Viking Therapeutics*		↓LDL-C ↓Liver fat content in patient with NAFLD [Erion et al. (72)]	Almost negligible side effects reported Phase 2b in progress (NCT4173065)

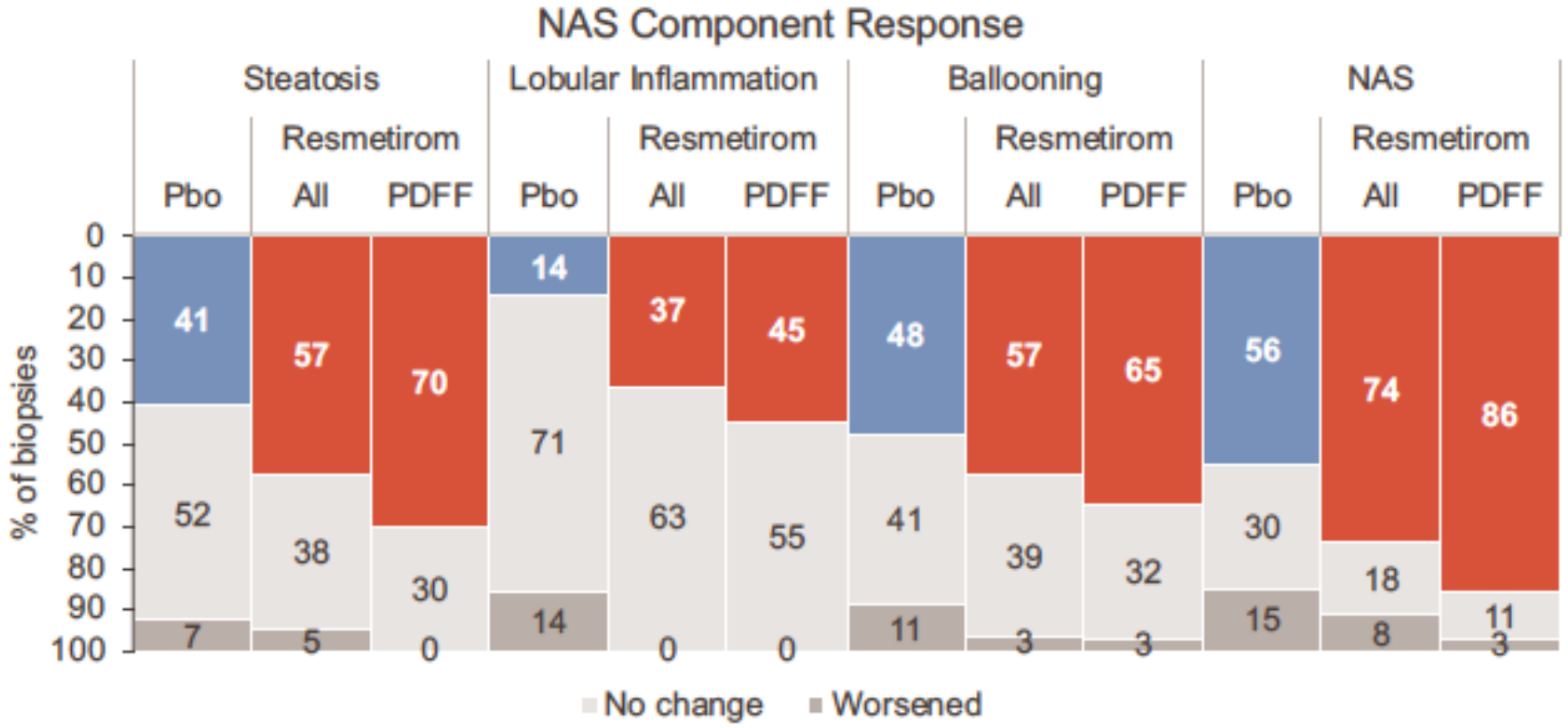
Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomized, double-blind, placebo-controlled, phase 2 trial





Harrison et al, Lancet. 2019;394:2012-24

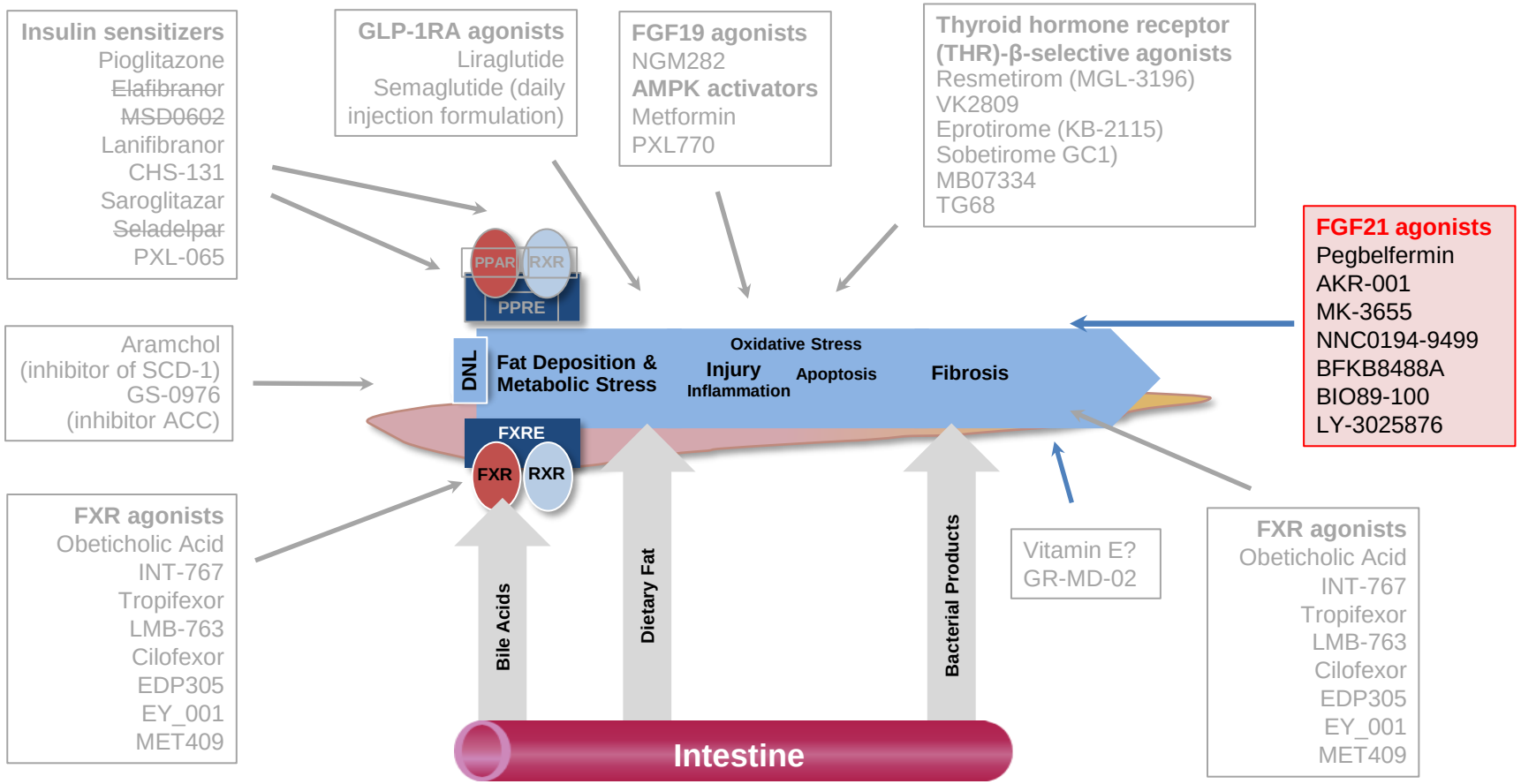
Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomized, double-blind, placebo-controlled, phase 2 trial



Conclusion: Resmetirom reduces liver fat content and improves histology.

Harrison et al, Lancet. 2019;394:2012-24

Potential Therapeutic Targets in NASH



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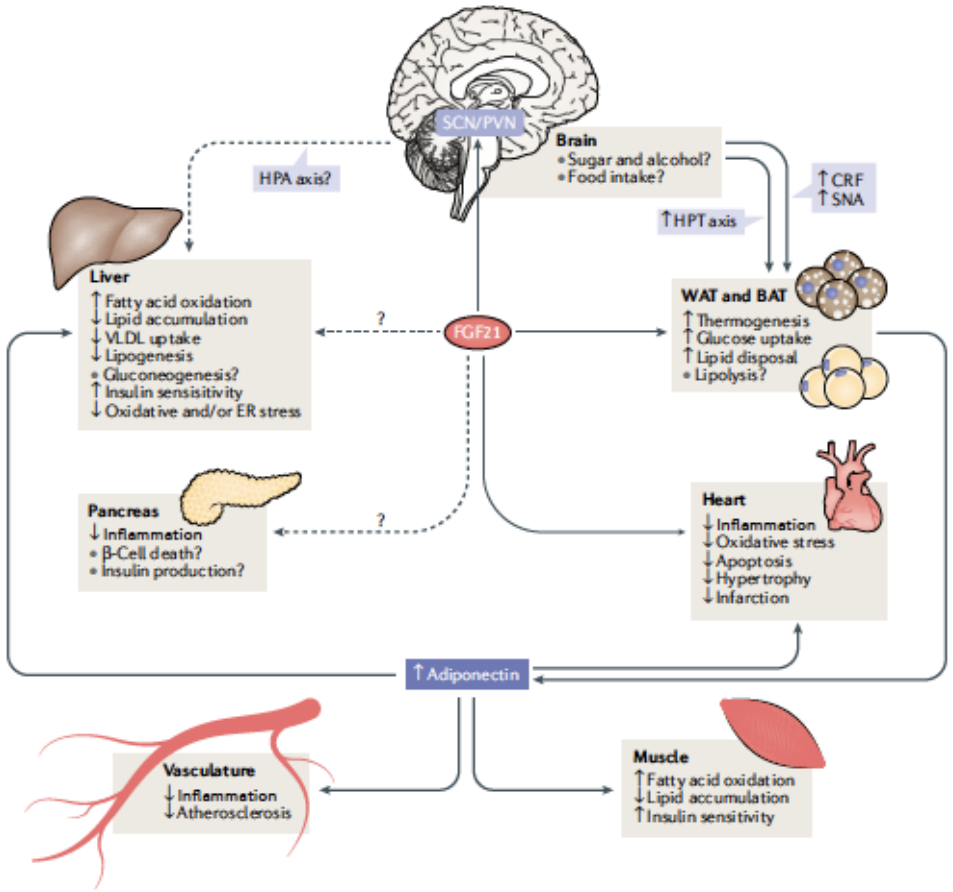
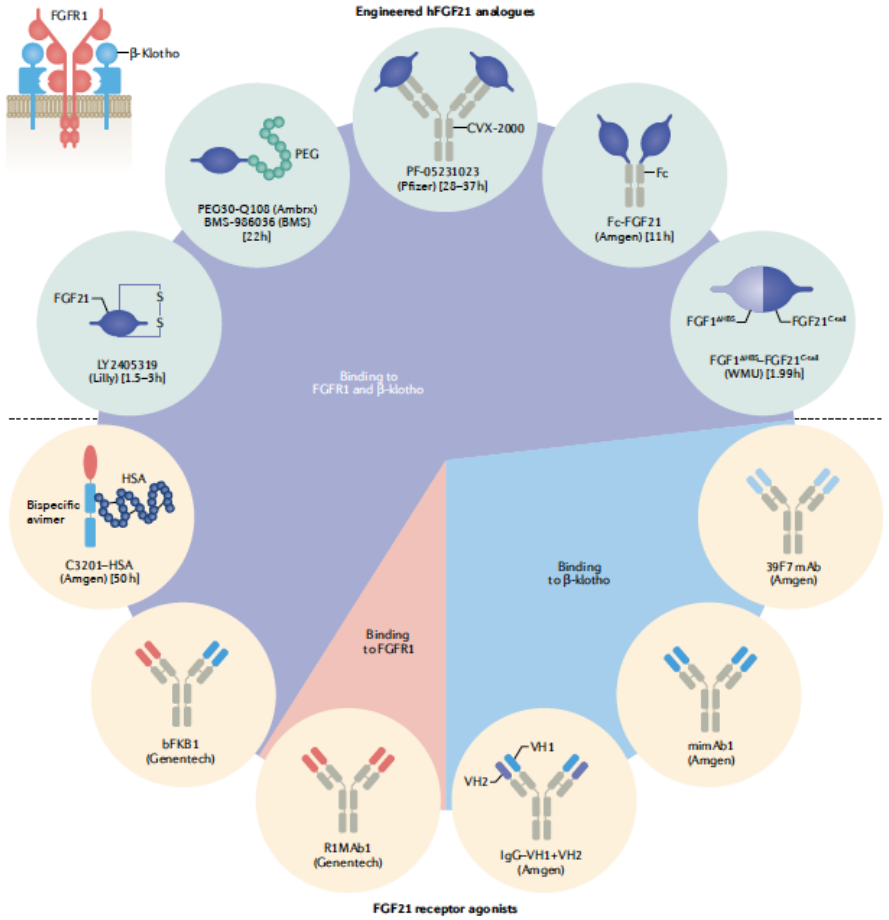
Adapted from Rotman et al. Gut. 2017;66:180–90

Targeting the FGF21 Pathway in NASH





Geng L, et al. Nature Reviews Endocrinology 2020;16:654–667.

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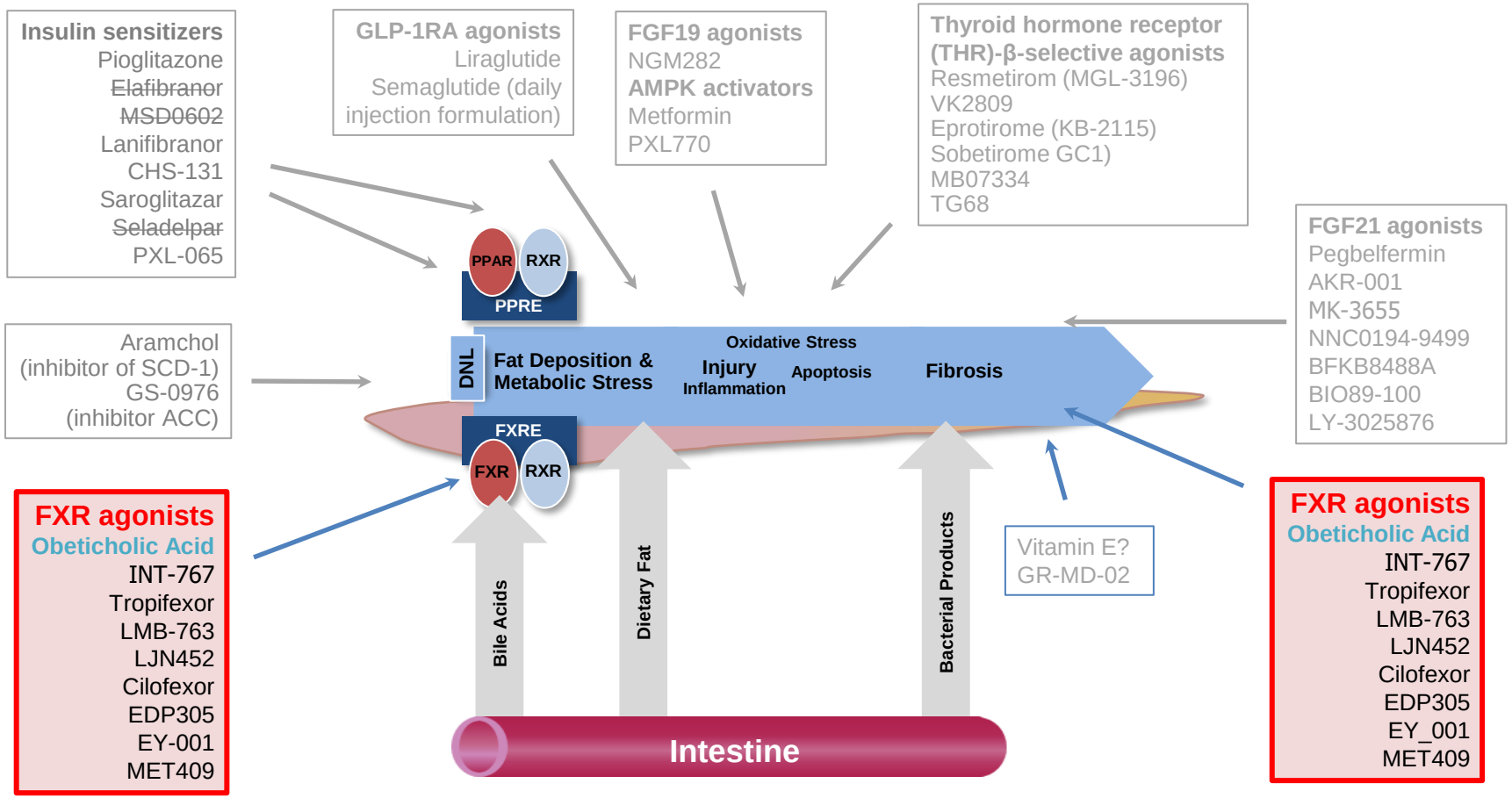
Potential Role of FXR Agonists in NASH

Kenneth Cusi, MD, FACP, FACE,
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida,
Gainesville, United States

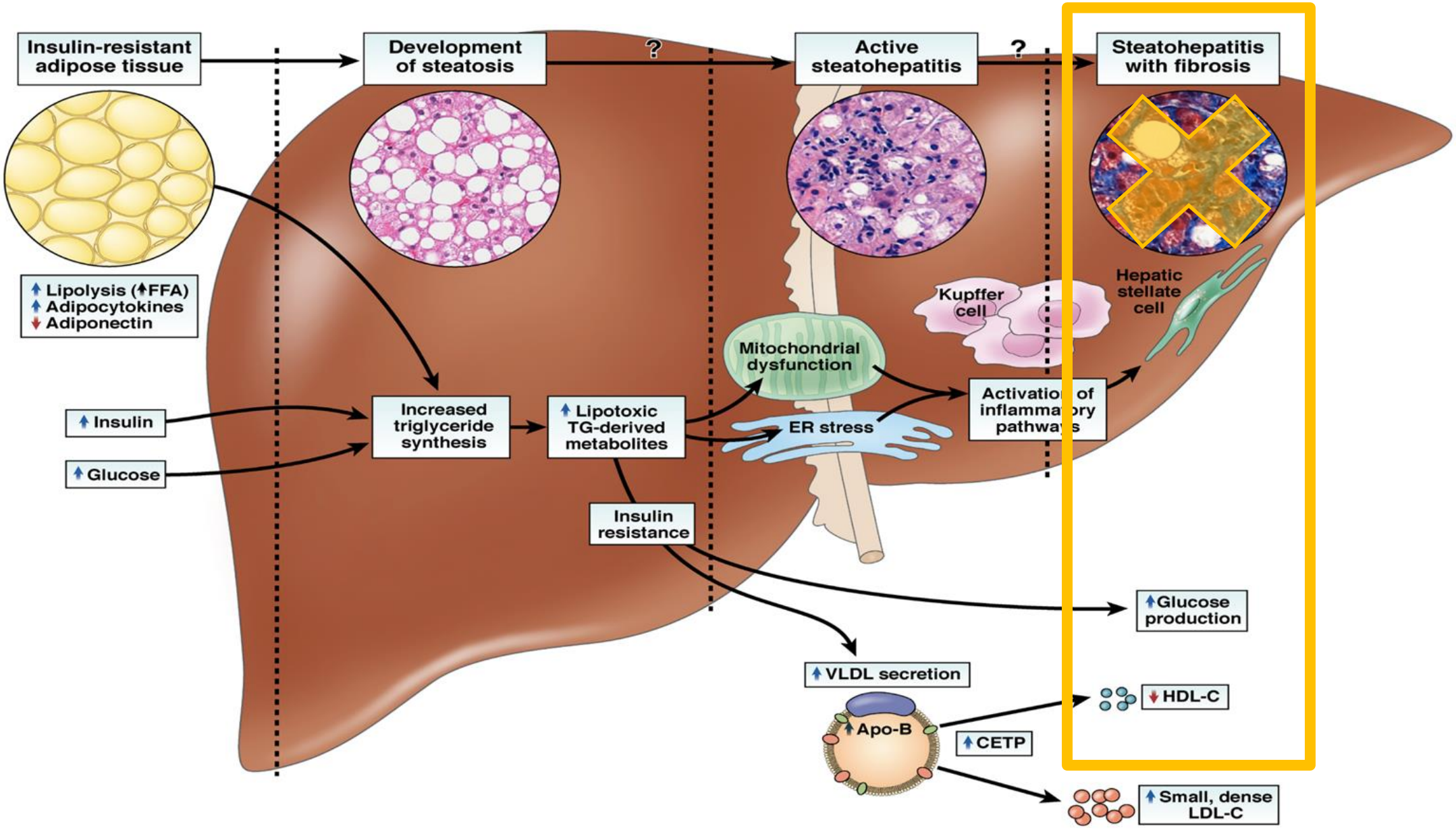
Potential Therapeutic Targets in NASH



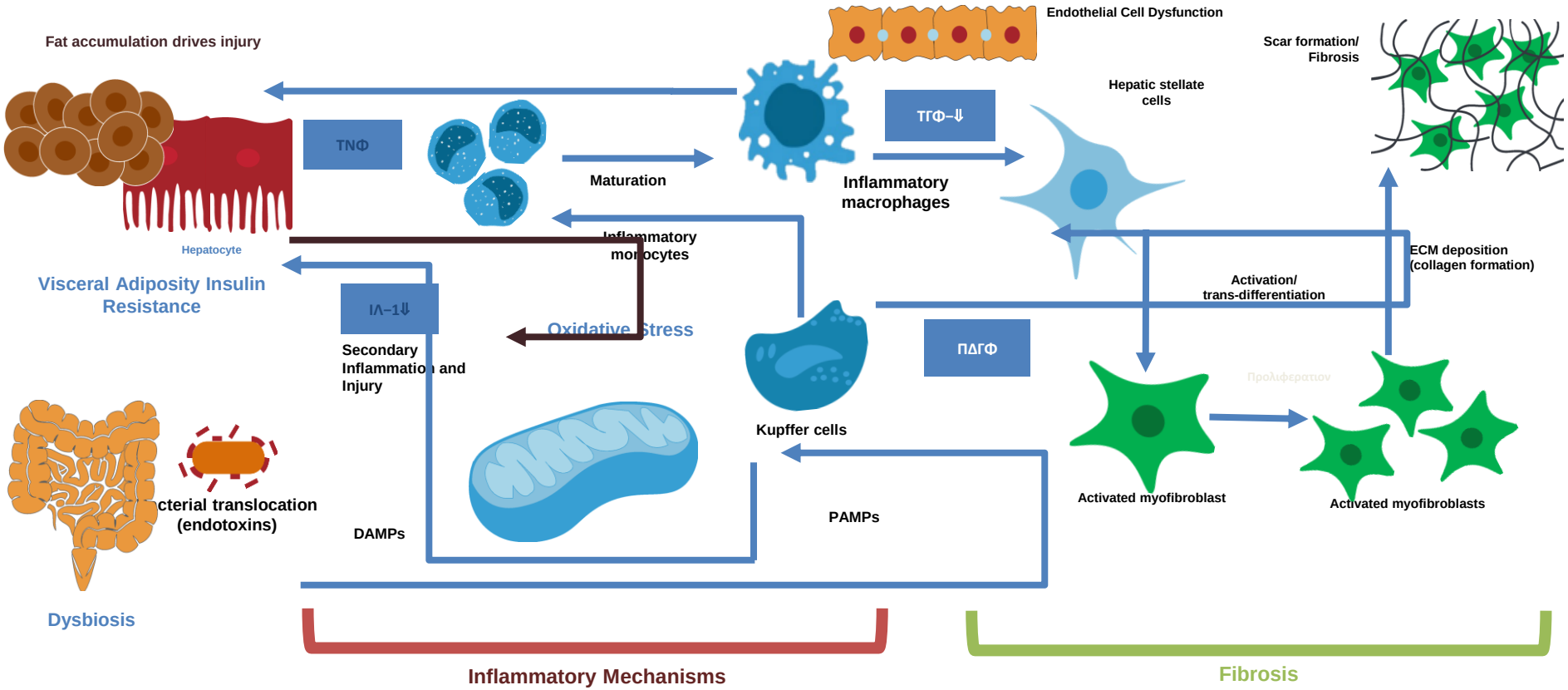
ACC, acetyl-CoA carboxylase; DNL, *de novo* lipogenesis; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; ; GLP-1RA, glucagon-like peptide-1 receptor agonist; MPC' mitochondrial pyruvate carrier; NASH, non-alcoholic steatohepatitis; PPAR' peroxisome proliferator-activated receptor; RXR, retinoid X receptor.

Adapted from Rotman et al. Gut. 2017;66:180–90

Can we Reduce Fibrosis Progression (or induce regression)?



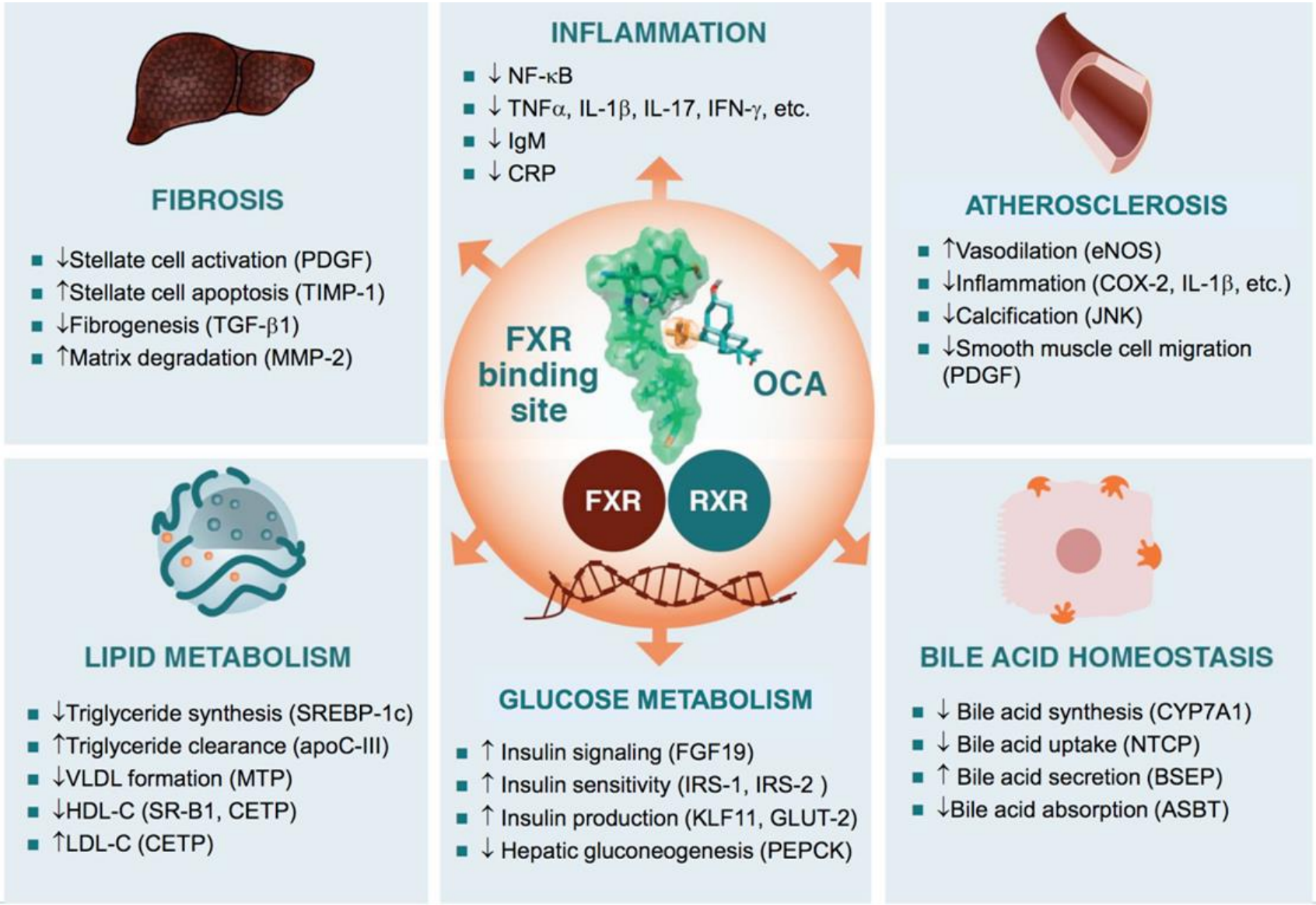
Pathogenesis of Liver Fibrosis in NASH



DAMP, danger-associated molecular patterns; ECM, extracellular matrix; IL-1β, interleukin-1beta; PAMP, pathogen-associated molecular patterns; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TNF-β, tumor necrosis factor-beta.

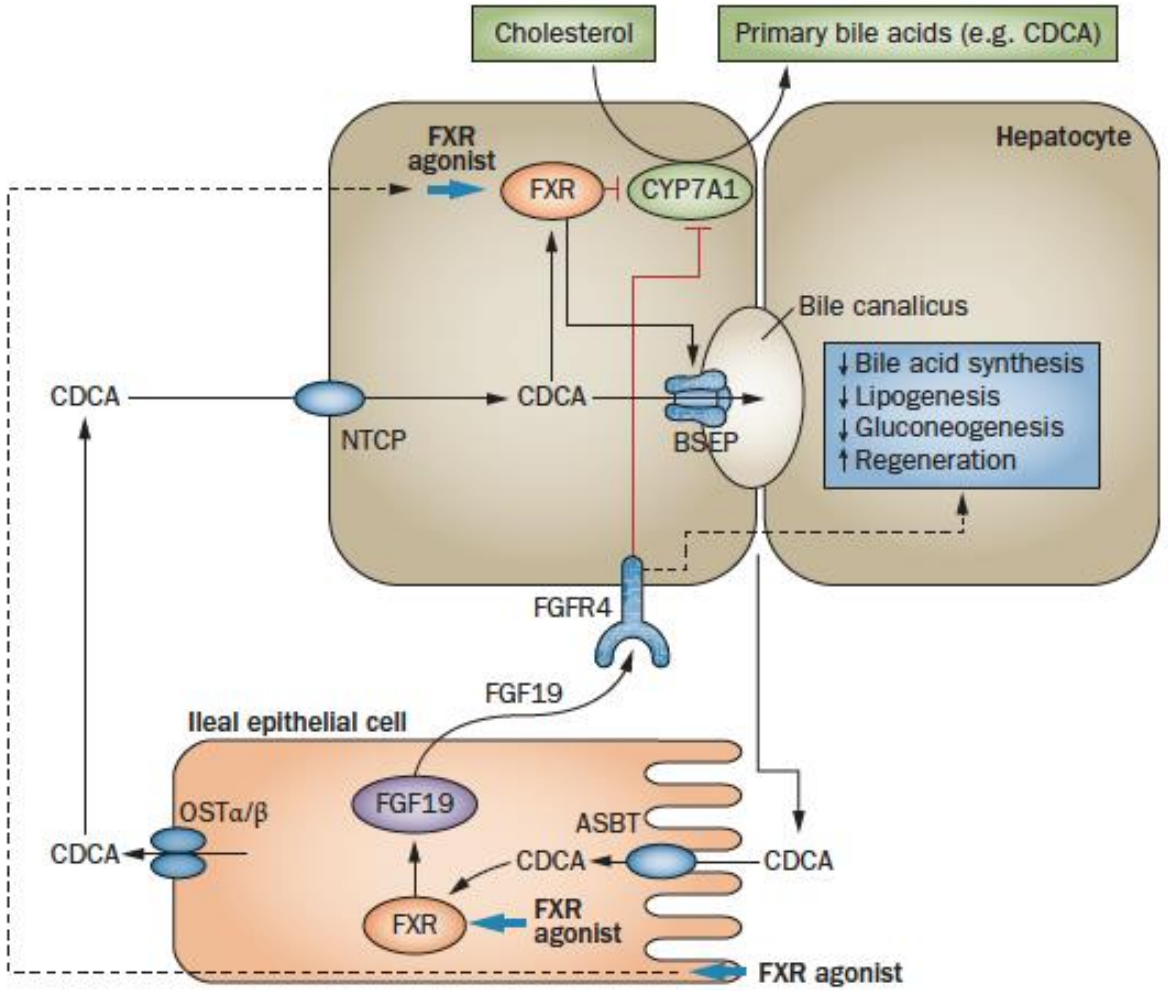
Benedict M, Zhang X. World J Hepatol. 2017;9(16):715-732; Bedossa P. Liver Int. 2017;37(suppl 1):85-89; Younossi ZM, et al. Hepatology. 2011;53(6):1874-1882.

Key FXR Pathways Described in Multiple Animal Models



Abenavoli L, et al. Pharmaceuticals. 2018;11(4); Adorini L, et al. Drug Discov Today. 2012;17:988-997; Makri E, et al. World J Gastroentrol. 2016;22:9039-9043.

Mechanisms of Action of Obeticholic Acid FXR Agonists



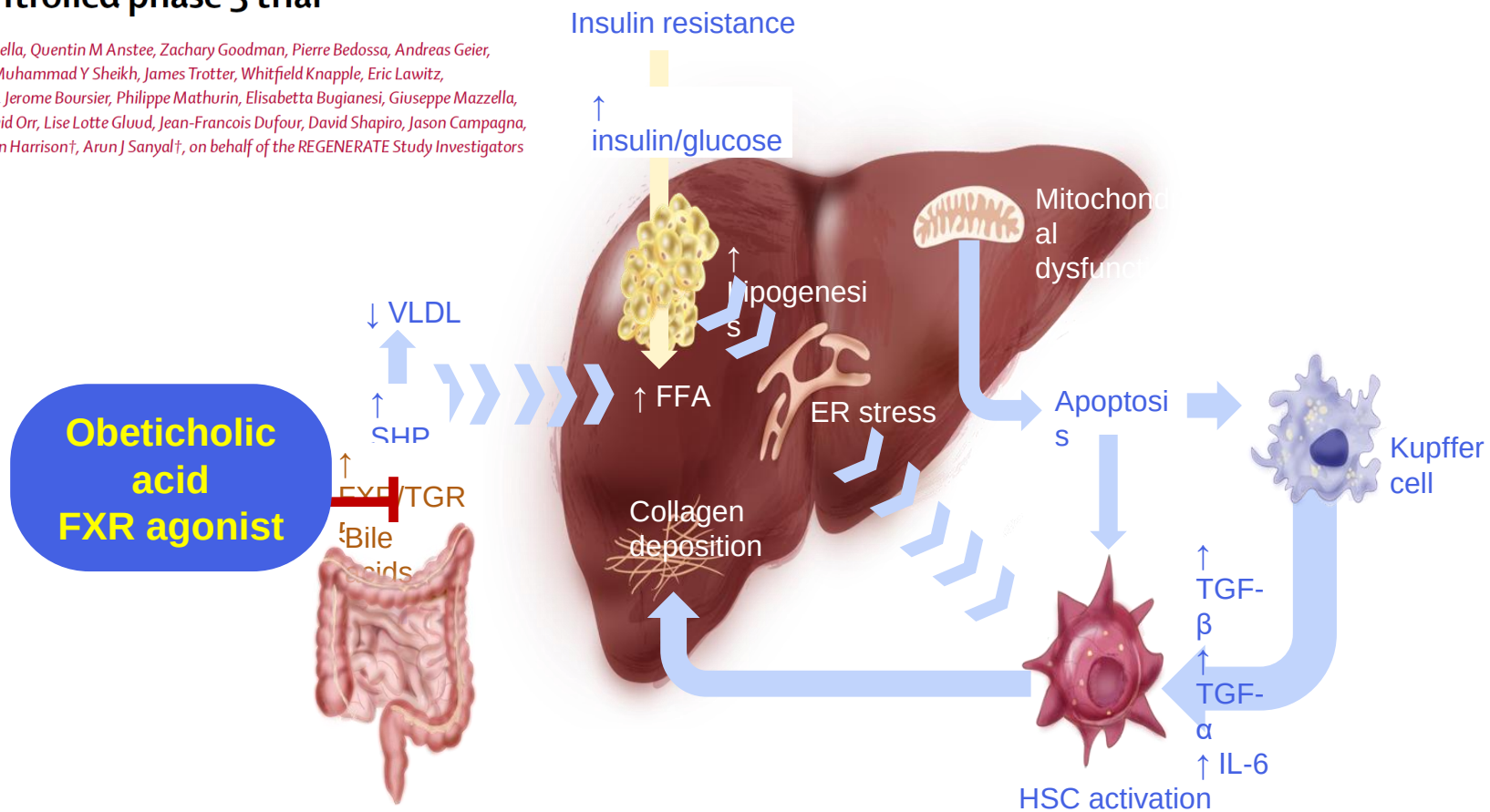
Schaap FG et al. Nat Rev Gastroenterol Hepatol. 2014 Jan;11(1):55-67.

Mechanisms of Action of Obeticholic Acid in NASH

Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial

Zobair M Younossi, Vlad Ratziu*, Rohit Loomba, Mary Rinella, Quentin M Anstee, Zachary Goodman, Pierre Bedossa, Andreas Geier, Susanne Beckebaum, Philip N Newsome, David Sheridan, Muhammad Y Sheikh, James Trotter, Whitfield Knapple, Eric Lawitz, Manal F Abdelmalek, Kris V Kowdley, Aldo J Montano-Loza, Jerome Boursier, Philippe Mathurin, Elisabetta Bugianesi, Giuseppe Mazzella, Antonio Olveira, Helena Cortez-Pinto, Isabel Graupera, David Orr, Lise Lotte Gluud, Jean-Francois Dufour, David Shapiro, Jason Campagna, Luna Zaru, Leigh MacConell, Reshma Shringarpure, Stephen Harrison†, Arun J Sanyal†, on behalf of the REGENERATE Study Investigators*

Lancet 2019; 394: 2184–96

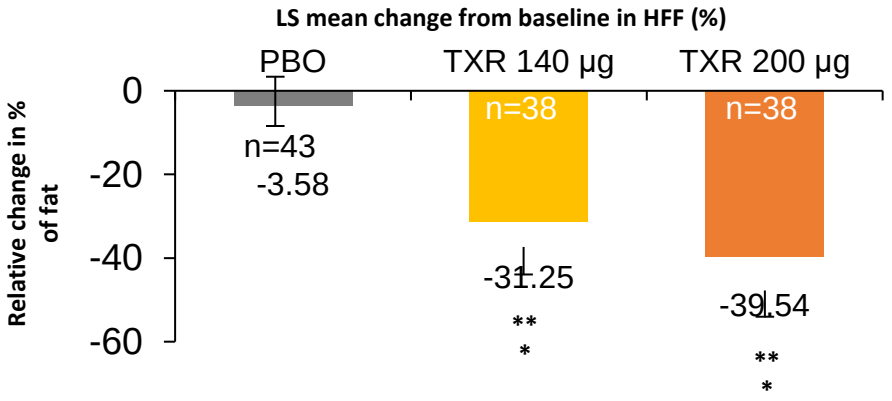


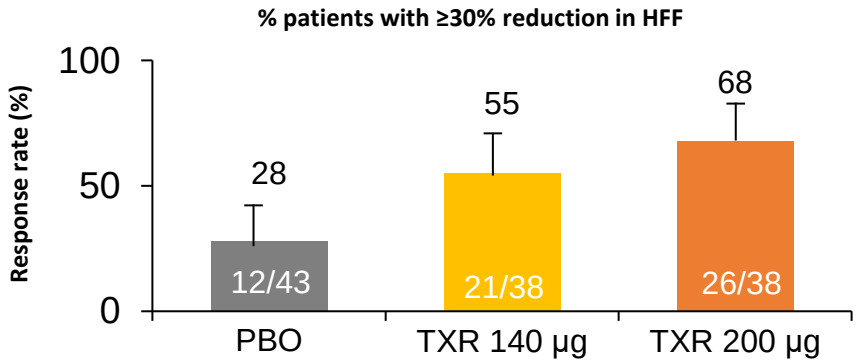
ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.

Konerman MA et al. J Hepatol. 2018;68:362-365.

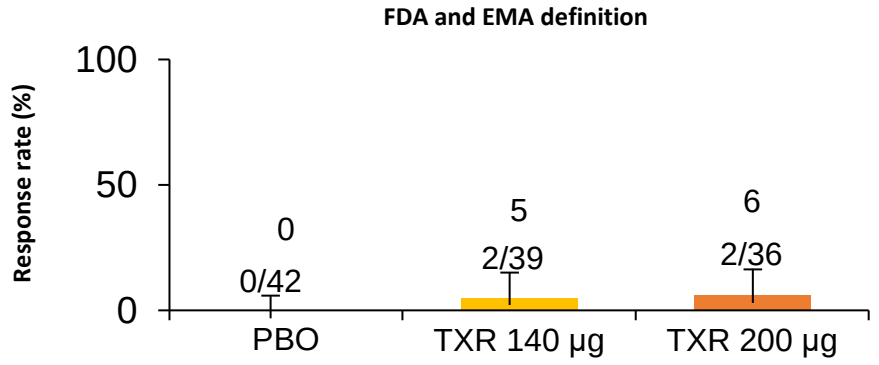
Safety and Efficacy of Tropifexor in Patients with NASH: 48-week results from FLIGHT-FXR study

Liver fat content (MRI-PDFF) at Week 48 - Significant decrease with tropifexor vs placebo

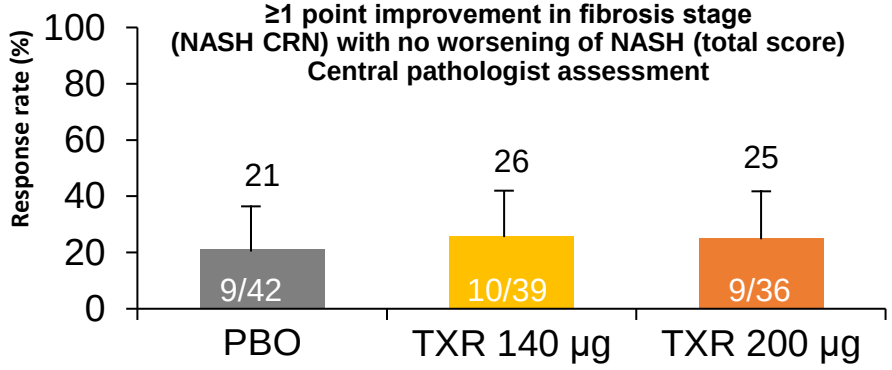




NASH resolution with no worsening of fibrosis



Effect on liver fibrosis



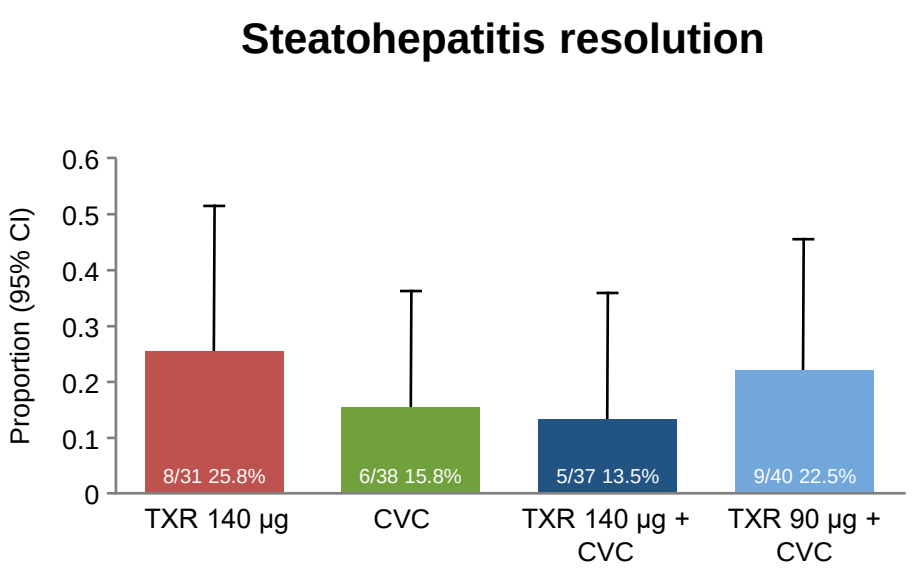
Conclusion: modest effect of tropifexor on NASH resolution or on fibrosis

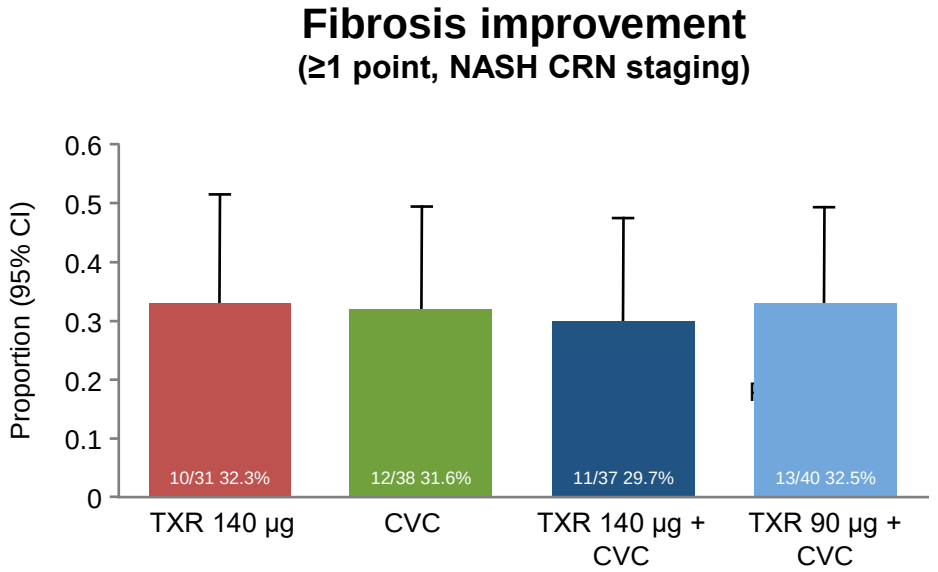
***p<0.001 vs PBO. Error bars show SE for LS mean change in liver fat. All other error bars show 95% CI.

Jean Lucas K, et al. AASLD 2020. #139

TANDEM study: Effects of tropifexor plus cenicriviroc (CVC) combination therapy on steatosis and fibrosis

Anstee QM, et al. AASLD 2021. #O142

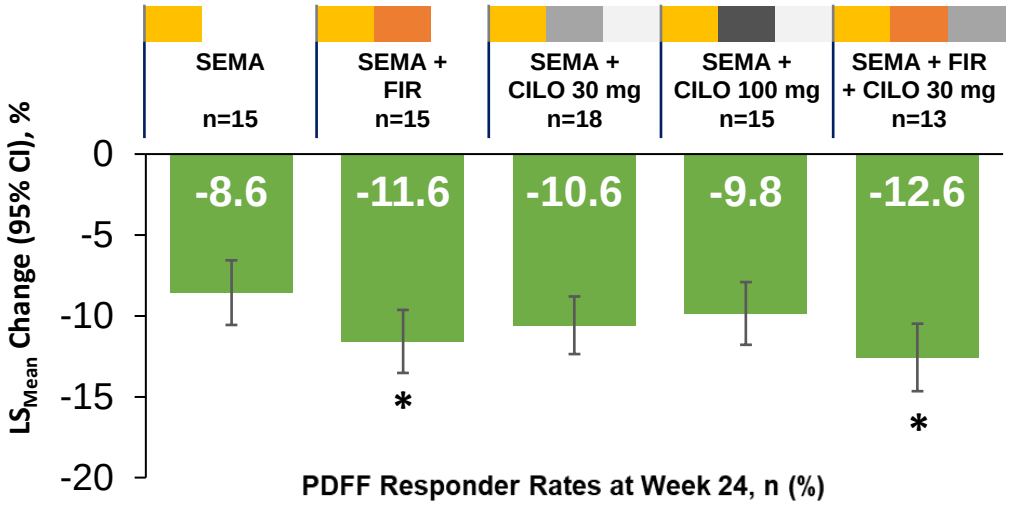




- Combination TXR + CVC was safe and well tolerated
- Pruritis most common TEAE (up to 40% with TXR)
- Combination therapy with TXR + **CVC failed to achieve primary histologic endpoint(s)**

Safety and Efficacy of Combination Therapies:
Semaglutide, Cilofexor, and Firsocostat in patients with NASH

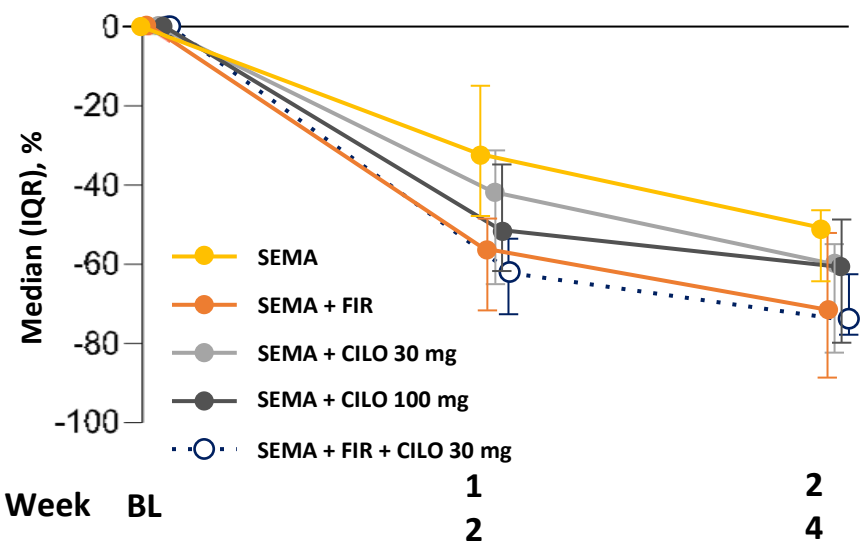
Absolute change in liver fat content (LFC) by MRI-PDFF at week 24



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 in LFC from baseline



Conclusion: Future opportunities in the combination of ”metabolic” and “antifibrotic” drugs (although this division is arbitrary)

Data analysis for LFC by MR-PDFF based on ANCOVA models adjusted for BL and diabetes status.
*p<0.05 vs SEMA alone.

Alkhouri N, et al. AASLD 2020. #LO2

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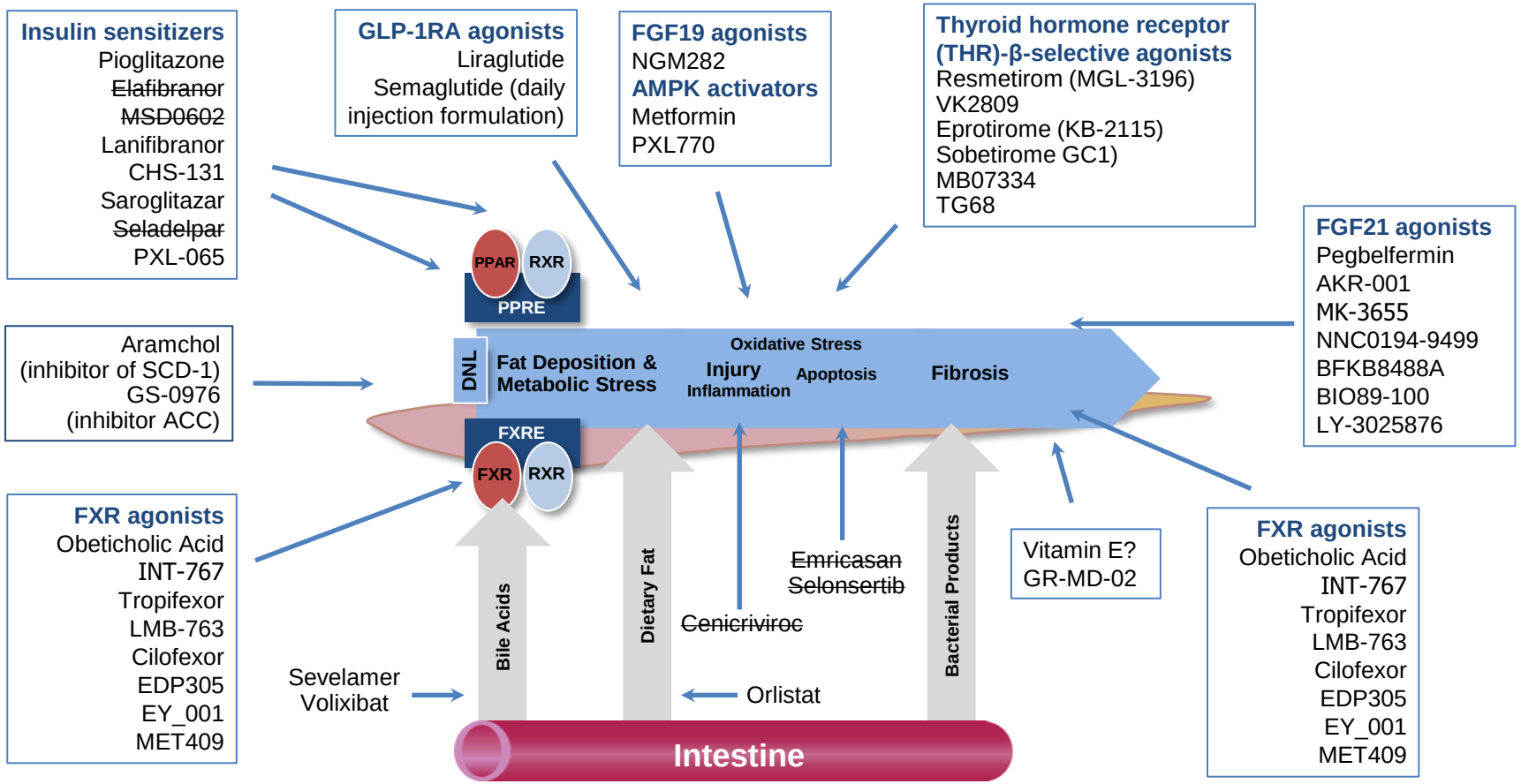
Summary of Novel Agents for the Treatment of NASH

Kenneth Cusi, MD, FACP, FACE,
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida,
Gainesville, United States

Potential Therapeutic Targets in NASH



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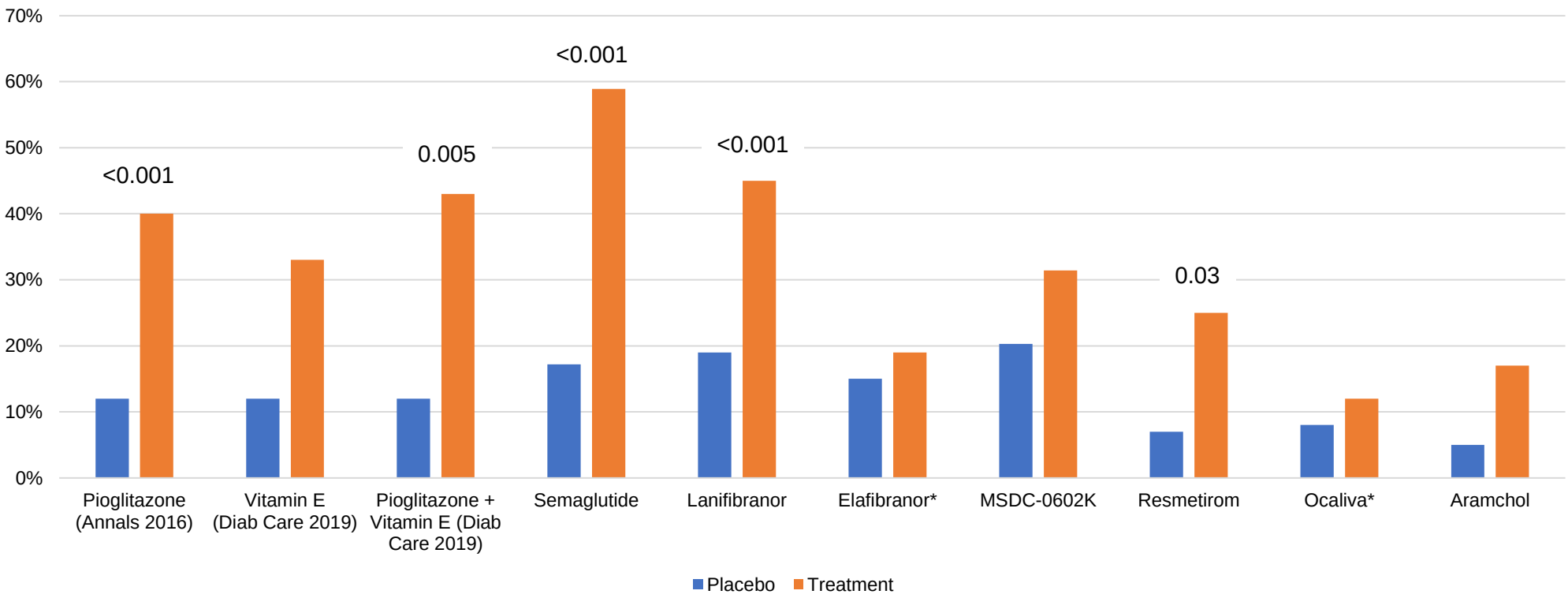
Adapted from Rotman et al. Gut. 2017;66:180–90

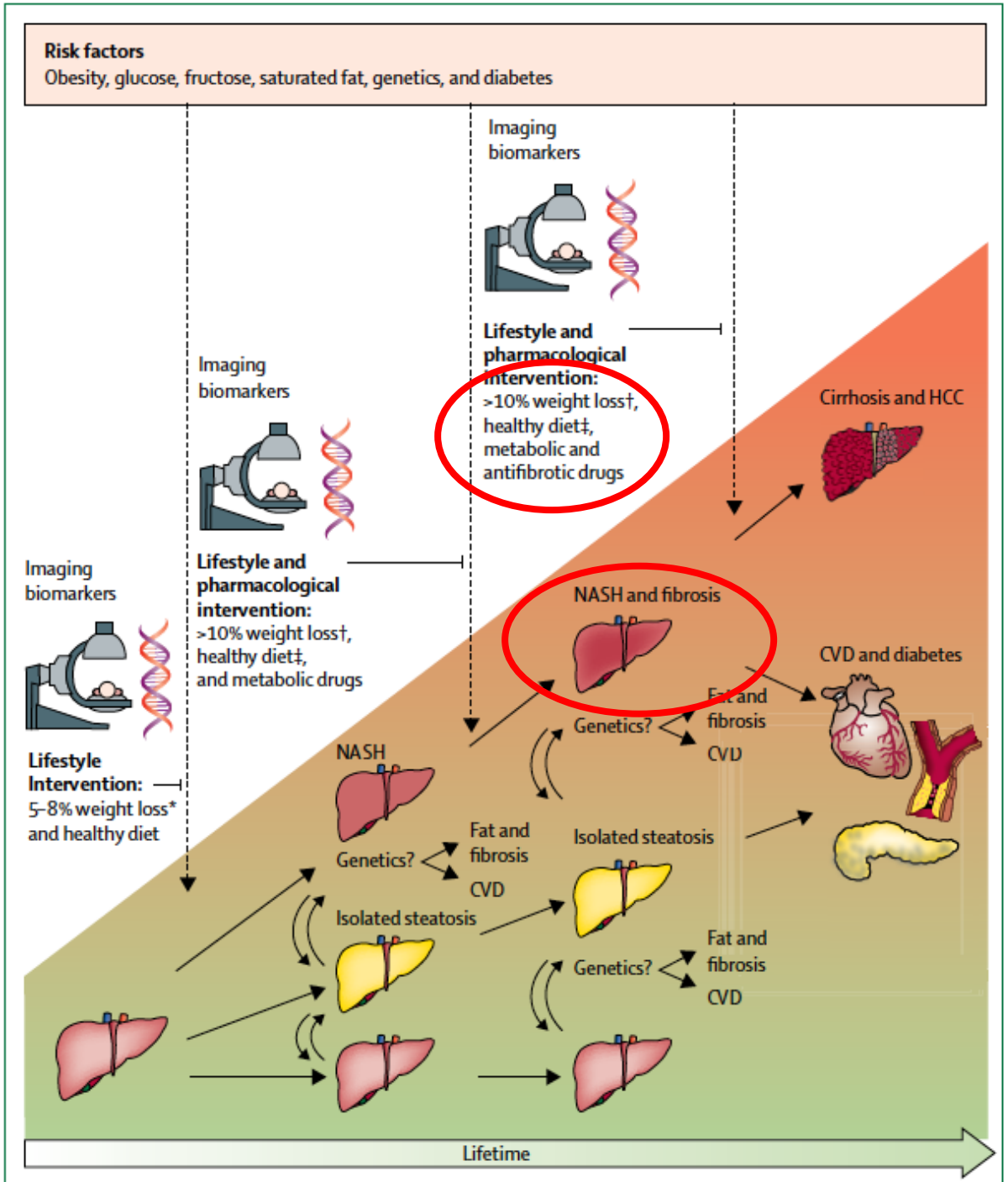
Resolution of NASH* with no worsening of fibrosis: Current and new agents in phase 2 or 3



*Resolution of NASH defined as a ballooning score of 0 and an inflammation score of 0-1 without worsening of fibrosis.

Cusi K (unpublished, 2020)

Take Home Message: Management Considerations and Targets in NASH



Stefan N, Cusi K.
Lancet Diabetes Endocrinol. 2019;7:313-324.

Take Home Messages: Treatment of NASH in 2022

- The obesity and diabetes epidemics will worsen in the coming decade and will fuel the epidemic of NASH and liver cirrhosis
- Cirrhosis may be prevented by early diagnosis (i.e., combining blood tests and imaging) and early treatment in primary care and endocrinology/diabetes clinics
- Many treatments to reverse NASH and/or fibrosis are in development, but treatment today should focus on:
  - Lifestyle changes that promote weight loss in people who are overweight or obese
  - Pharmacological treatments that reverse obesity (like GLP-RAs) or dysfunctional adipose tissue/insulin resistance (like pioglitazone).

Cusi K, 2022 (unpublished)