Overview of the Clinical Trial Data on Non-alcoholic Steatohepatitis (NASH)

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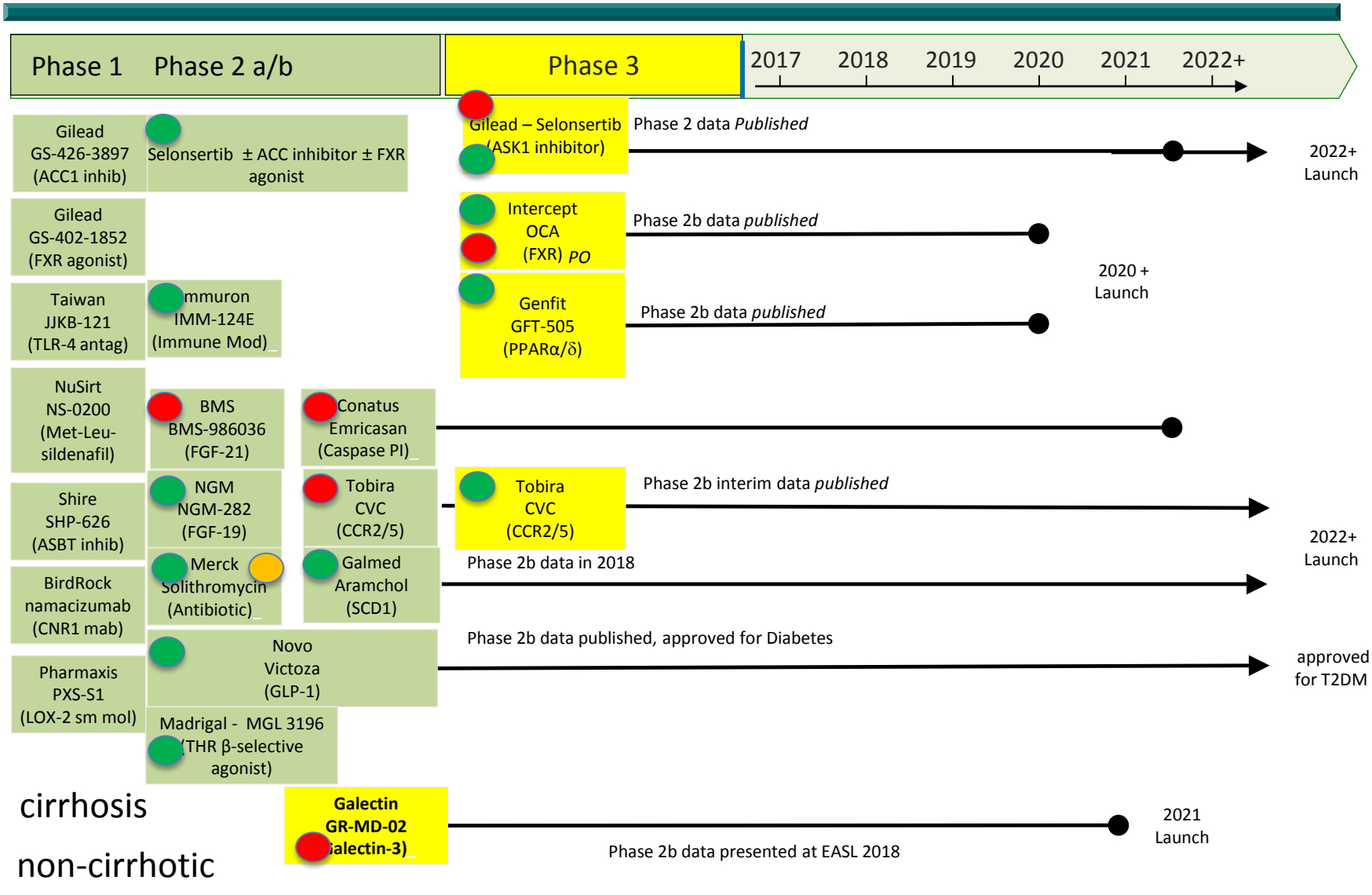
SAINT LOUIS UNIVERSITY

SAINT LOUIS UNIVERSITY LIVER CENTER

COI

- Consultant/Advisor:
  - Allergan, Arrowhead, Blade, Boehringer Ingleheim, BMS, Coherus, Consynance, Enanta, Gelesis, Gilead, Intercept, Lipocine, Madrigal, Medimmune, Merck, Metacrine, NGM, pH-Pharma, Prometheus

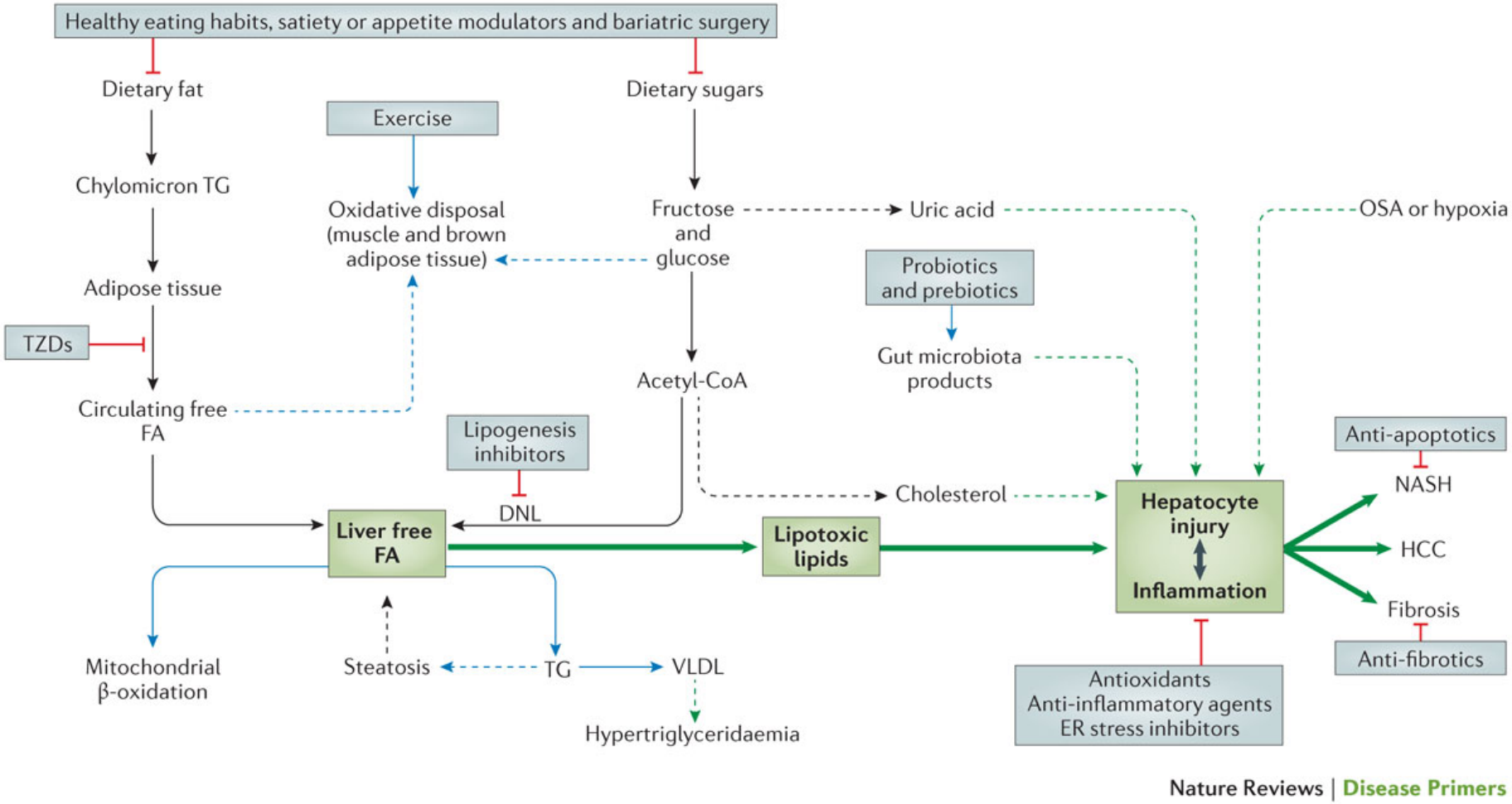
NASH Pipeline in 2018 - Front Runners



Represents earliest and most aggressive approval timelines.

Slide courtesy of Naga Chalasani (IU)

The lipotoxicity model of NASH and targets for therapy



Brunt, E. M. *et al.* (2015) Nonalcoholic fatty liver disease *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.80

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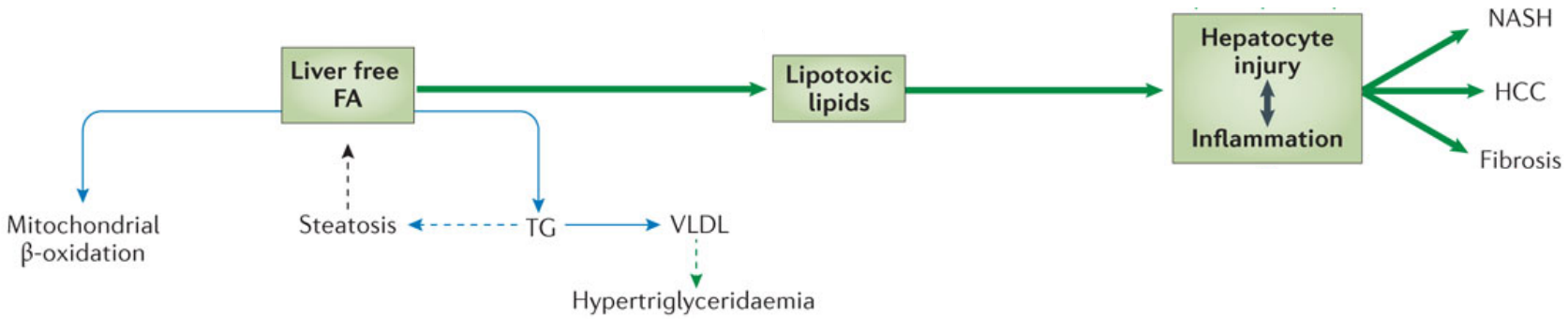

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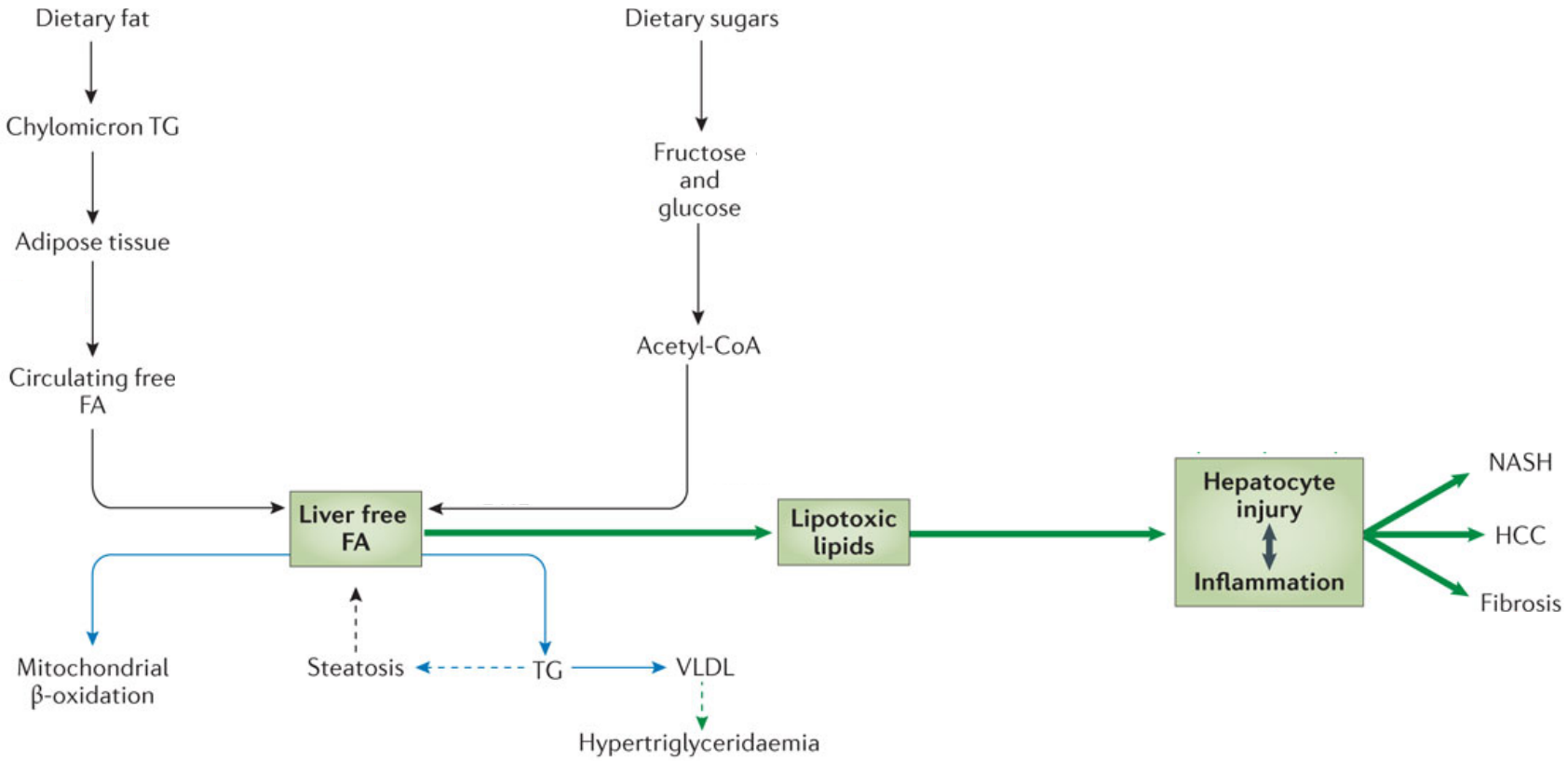
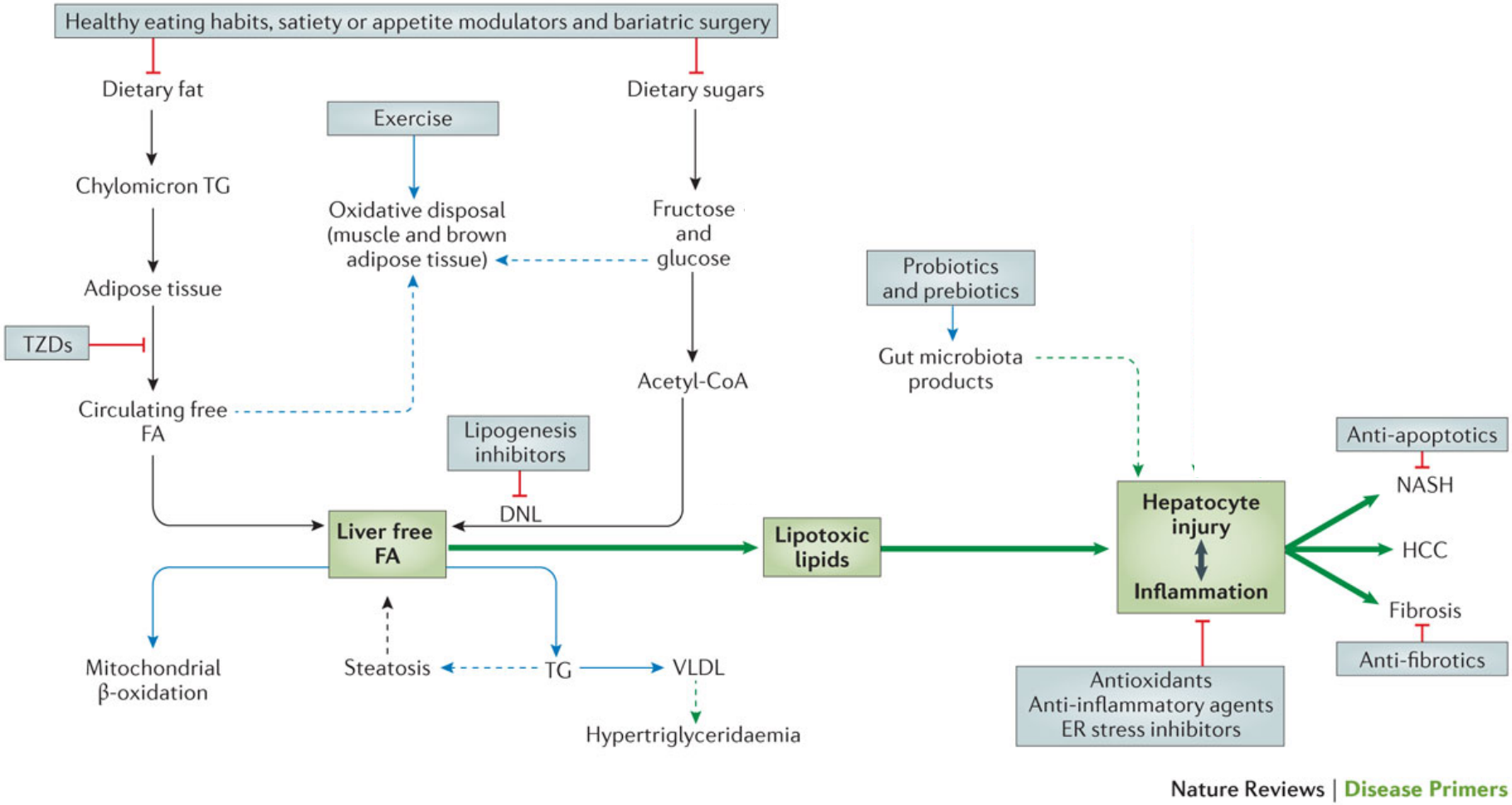
The lipotoxicity model of NASH and targets for therapy



Brunt, E. M. *et al.* (2015) Nonalcoholic fatty liver disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.80

Targets of therapy



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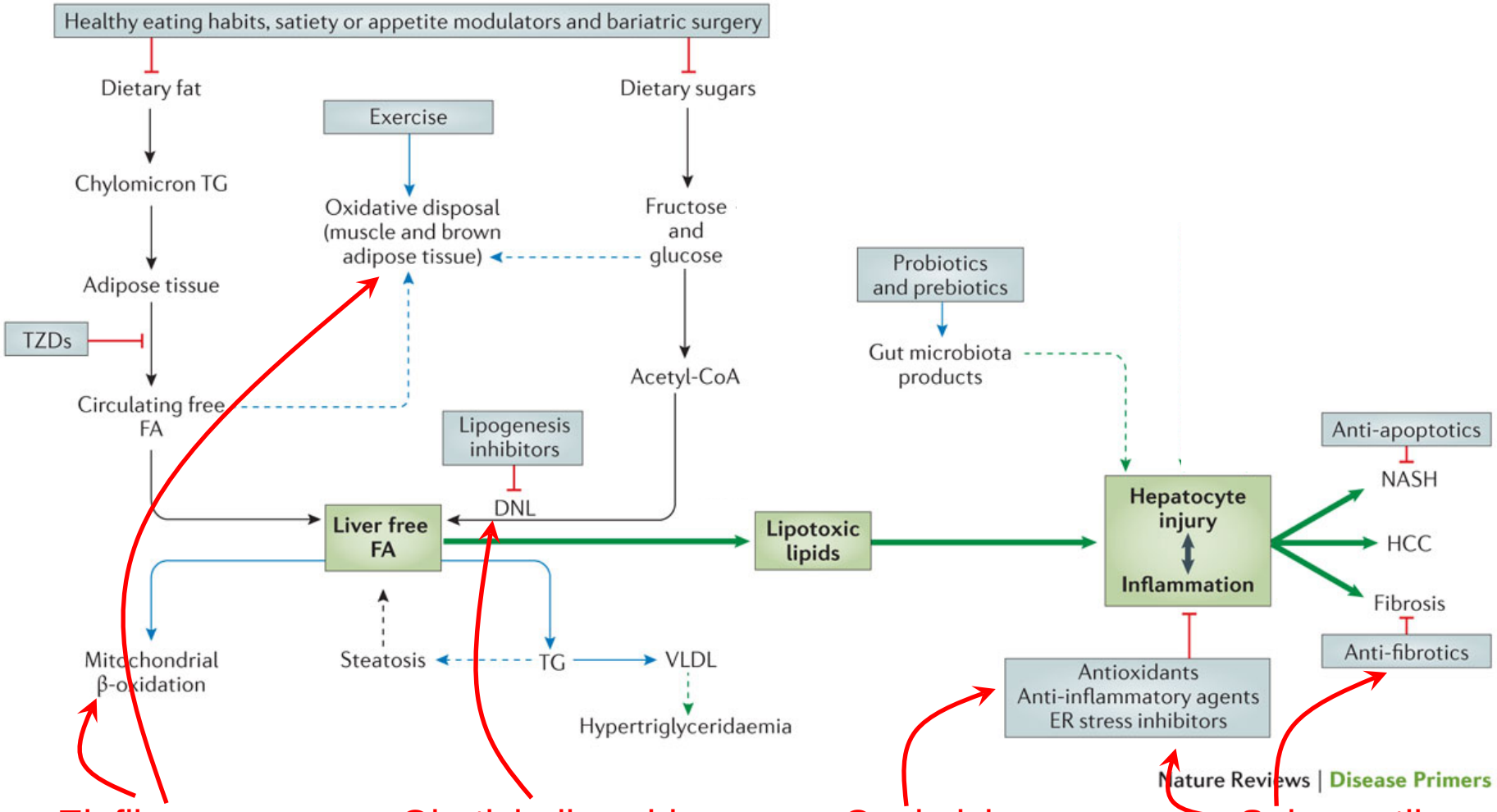
Drugs in Phase 3 trials



Elafibranor (PPARα/δ)

Obeticholic acid (FXR)

Cenicriviroc (CCR2/5)

Selonsertib (ASK-1 inhib)

Brunt, E. M. *et al.* (2015) Nonalcoholic fatty liver disease *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.80

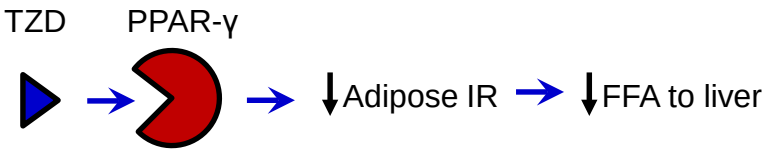
NASH Ongoing Phase 3 trials

- Obeticholic acid: REGENERATE & REVERSE (Intercept)
- Elafibranor: RESOLVE-IT (Genfit)
- Selonsertib: STELLAR 3 & STELLAR 4 (Gilead)
- Cenicriviroc: AURORA (Allergan)

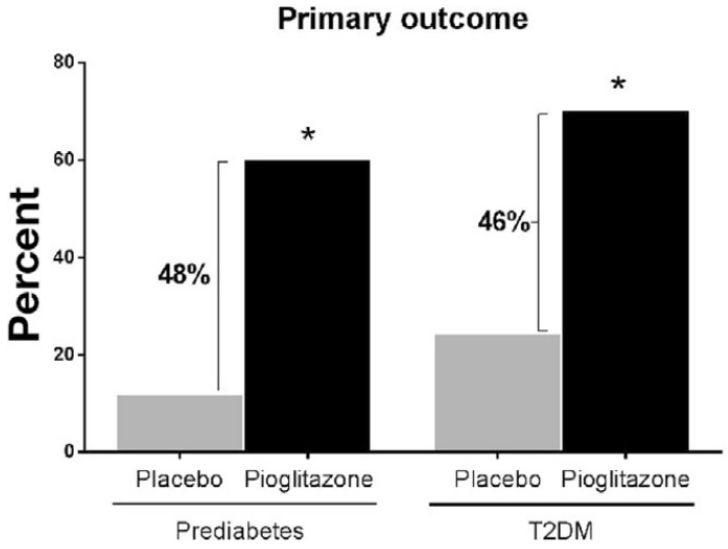
*All are **Phase3/4 adaptive design** with **histological end points for Subpart H conditional approval** followed by **clinical end points for full approval***

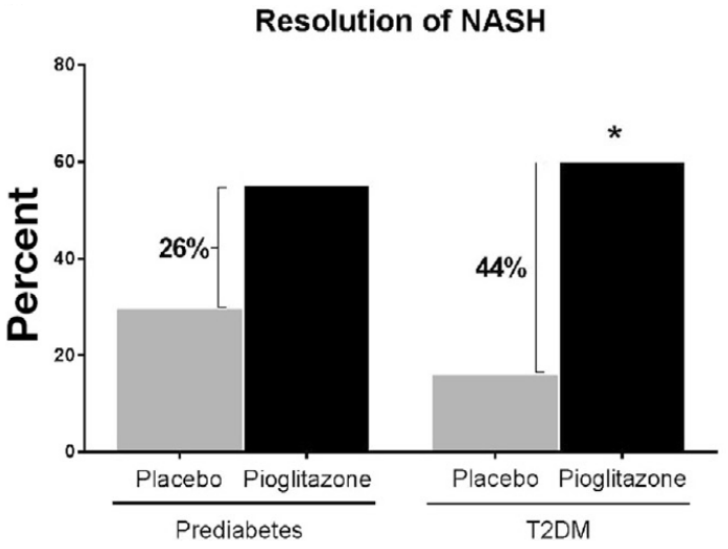
Slide courtesy of Naga Chalasani (IU)

Pioglitazone for NASH



- Pioglitazone 45 mg daily + diet x 18 months
  - N = 101
  - 1º endpoint: NAS improvement >= 2 and no worsening fibrosis
  - Diabetic subjects (n = 52) had a better response
  - Improvements maintained in a 18 month open label follow up study
    - Cusi et al, Ann Intern Med 2016;165:305-315
  - AASLD and EASL guidance: consider in non-cirrhotics with **biopsy** dx of NASH





Bril et al, Clin Gastroenterol Hepatol 2018;16:558-566

THE LANCET

Published Online November 7, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61933-4

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

*Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network**

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NATIONAL CANCER INSTITUTE

Partial funding for the trial, obeticholic acid, and placebo were provided by Intercept Pharmaceuticals under a Collaborative Research and Development Agreement with the NIDDK.

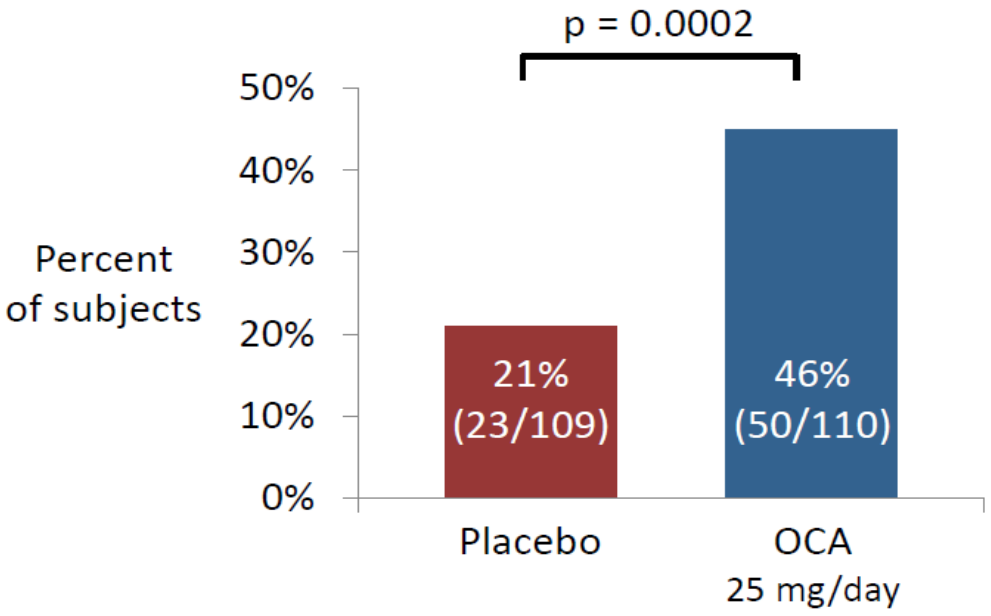
The FLINT trial

- Obeticholic acid (OCA), 25 mg orally daily vs placebo
- Inclusion: adults with NASH on biopsy, NAS ≥ 4; Exclusion: cirrhosis
- N = 283 patients randomized at 8 clinical centers
- 72 weeks of treatment
- Biopsy ≤ 3 mo. before treatment and after 72 weeks
- Primary endpoint
  - Improvement in NAFLD activity score ≥ 2 pts with no worsening of fibrosis

Neuschwander-Tetri et al, The Lancet, http://dx.doi.org/10.1016/S0140-6736(14)61933-4

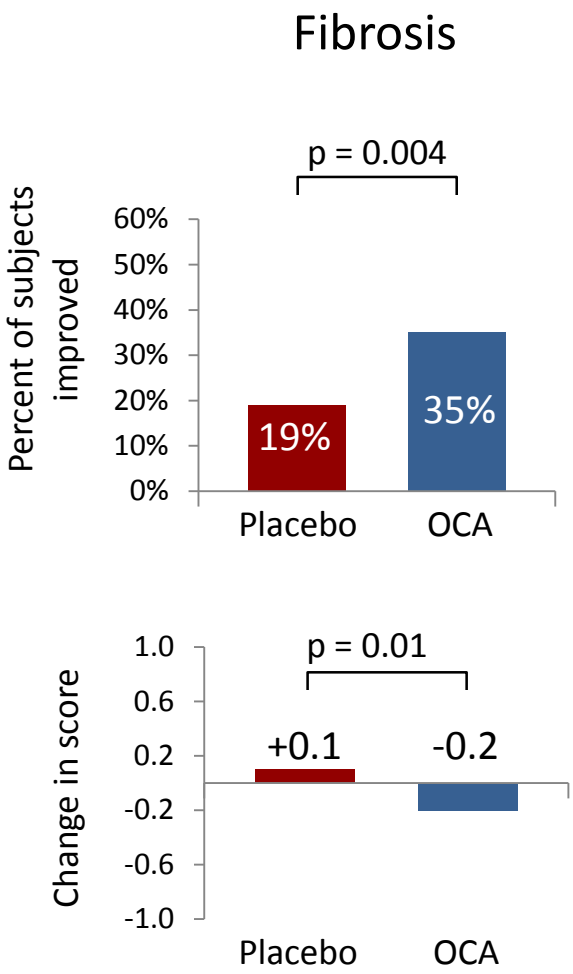
FLINT primary endpoint

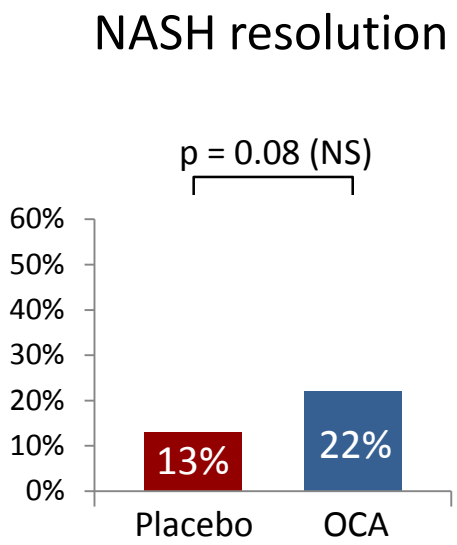
- Improvement in NAFLD activity score* (NAS) ≥ 2 pts
  - * NAS = steatosis grade (0-3) + inflammation grade (0-3) + ballooning grade (0-2)
- No worsening of fibrosis
- Results:



Neuschwander-Tetri et al, The Lancet, http://dx.doi.org/10.1016/S0140-6736(14)61933-4

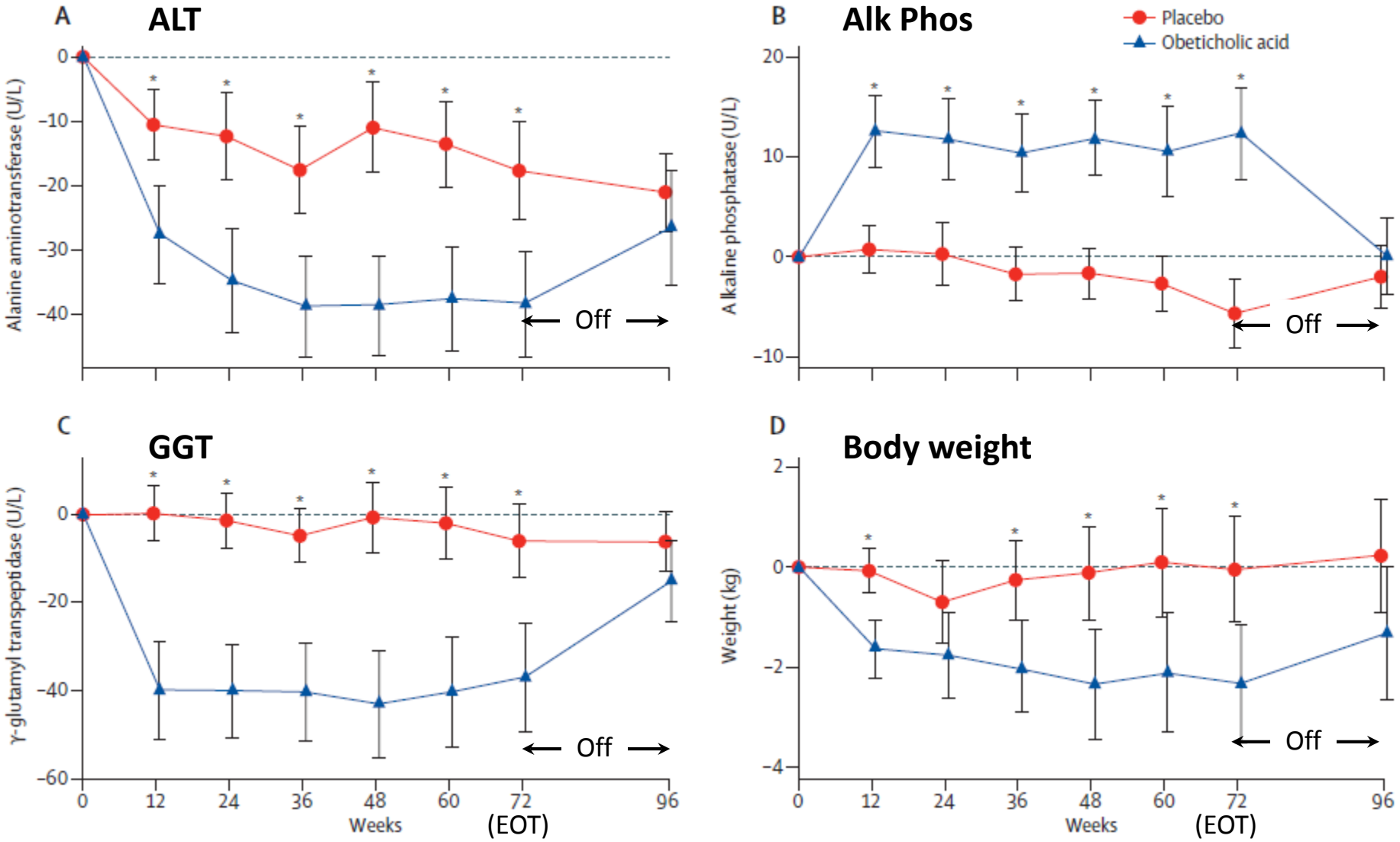
Improvement in fibrosis and NASH resolution





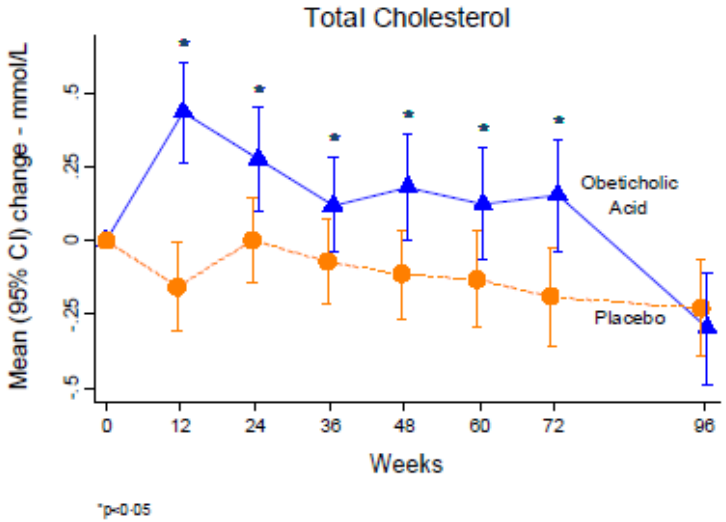
Neuschwander-Tetri et al, The Lancet, http://dx.doi.org/10.1016/S0140-6736(14)61933-4

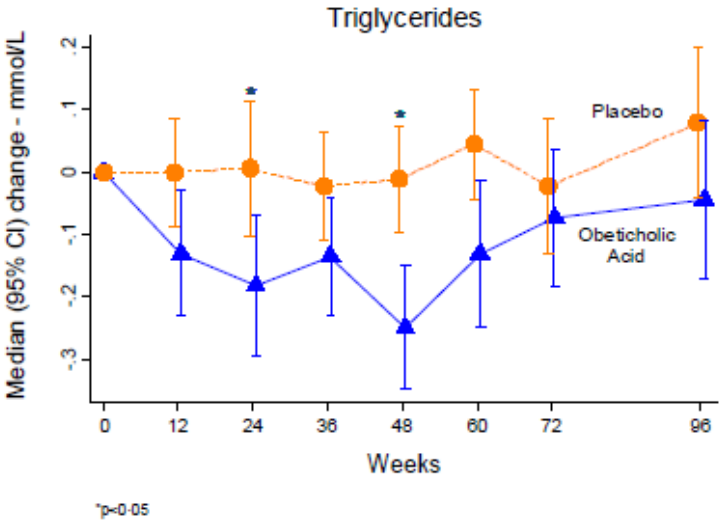
Enzymes and body weight

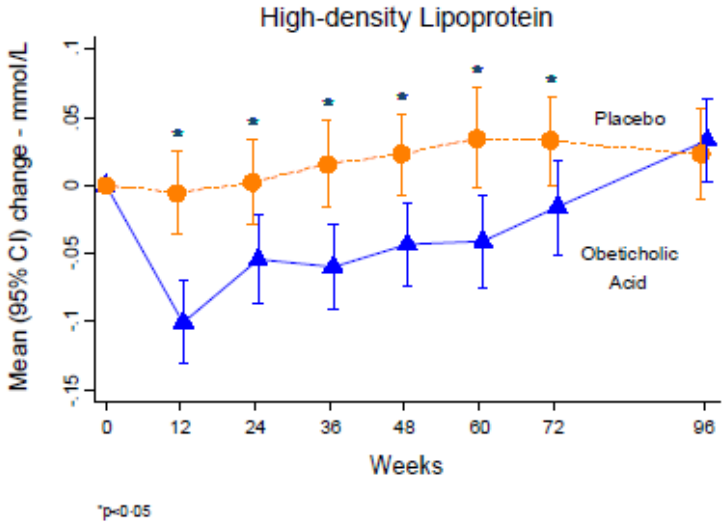


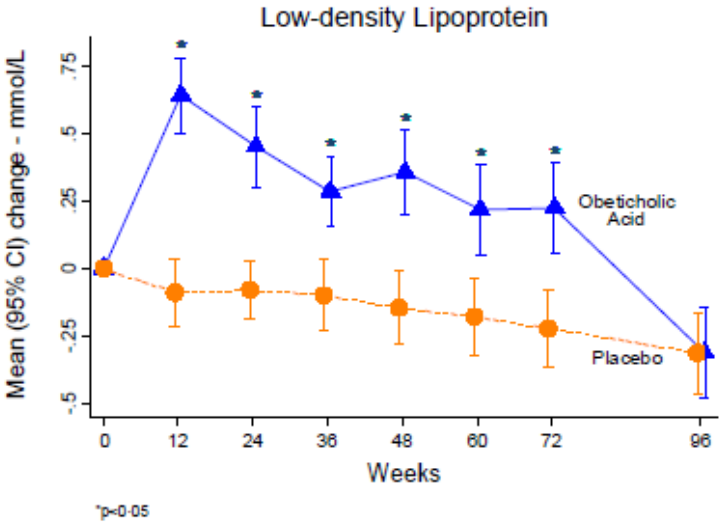
Neuschwander-Tetri et al, The Lancet, http://dx.doi.org/10.1016/S0140-6736(14)61933-4

Serum lipids





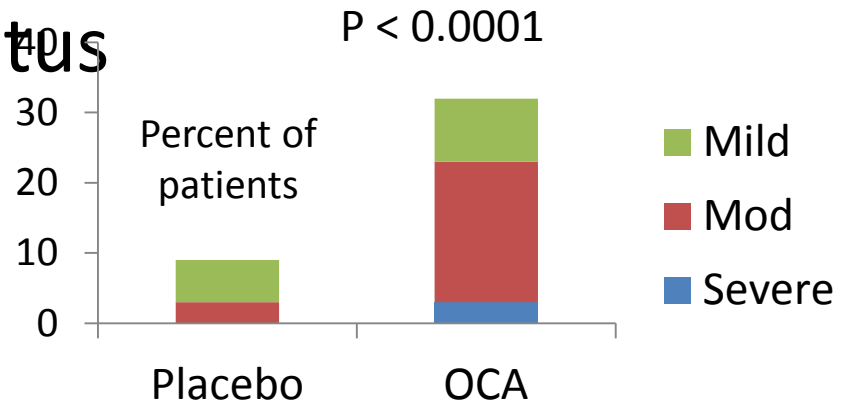




Neuschwander-Tetri et al, The Lancet, http://dx.doi.org/10.1016/S0140-6736(14)61933-4

Adverse events

- 6 severe adverse events in obeticholic acid group
  - 4 severe pruritus (1 stopped treatment)
  - 1 hypoglycemia
  - 1 possible cerebral ischemia (dysarthria and dizziness)
- Moderate or severe pruritus
  - 23% in obeticholic acid
  - 6% in placebo



Neuschwander-Tetri et al, The Lancet, http://dx.doi.org/10.1016/S0140-6736(14)61933-4

Gastroenterology 2016;150:1147–1159

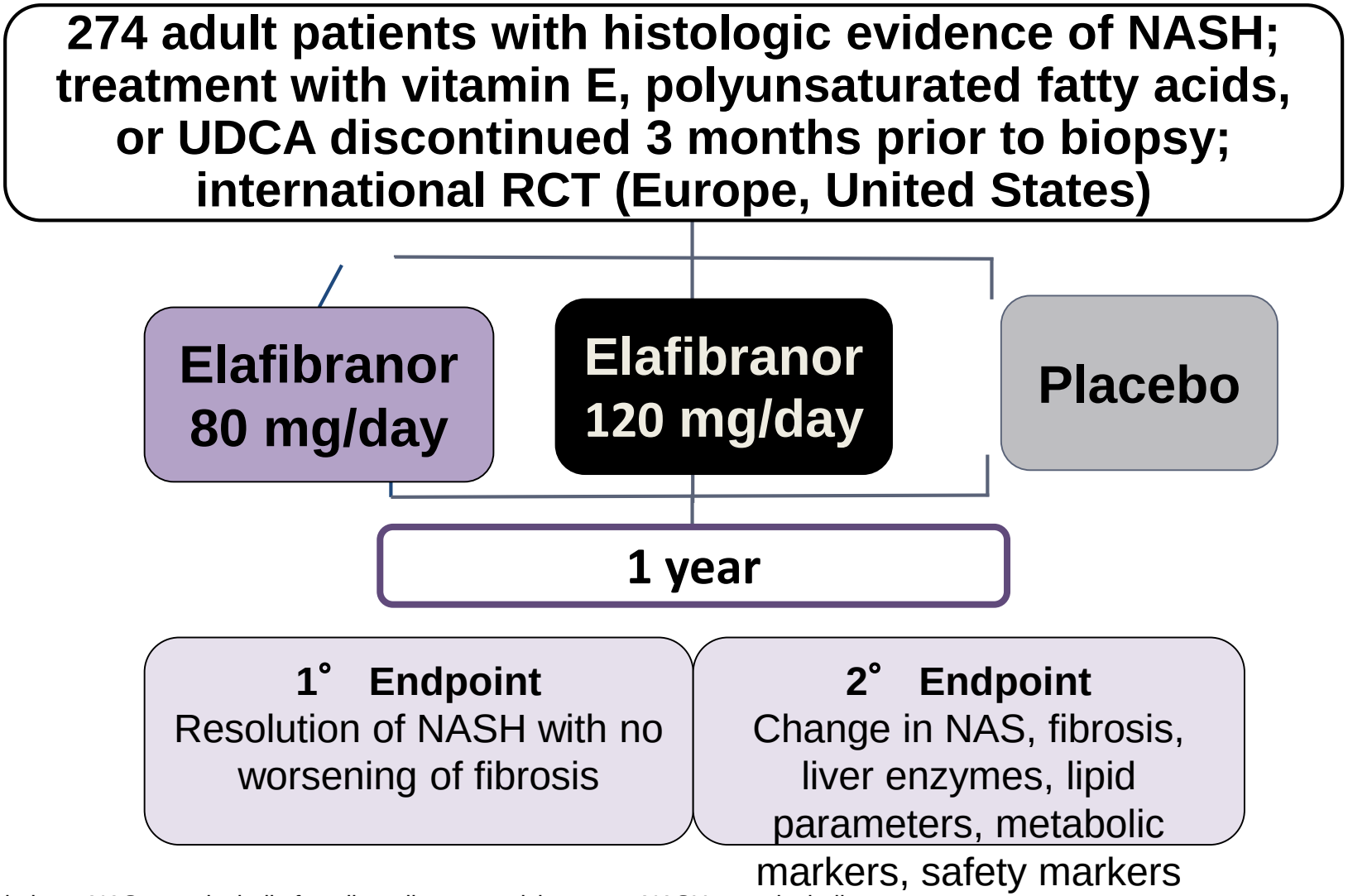
CLINICAL—LIVER

Elafibranor, an Agonist of the Peroxisome Proliferator—Activated Receptor—α and —δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening

Vlad Ratziu,[1,2] Stephen A. Harrison,[3] Sven Francque,[4] Pierre Bedossa,[5] Philippe Lehert,[6,7] Lawrence Serfaty,[8] Manuel Romero-Gomez,[9] Jérôme Boursier,[10] Manal Abdelmalek,[11] Steve Caldwell,[12] Joost Drenth,[13] Quentin M. Anstee,[14] Dean Hum,[15] Remy Hanf,[15] Alice Roudot,[15] Sophie Megnien,[15] Bart Staels,[16] and Arun Sanyal,[17] on behalf of the GOLDEN-505 Investigator Study Group

Slide courtesy of Naga Chalasani (IU)

Elafibranor—Phase IIb GOLDEN Trial



Abbreviations: NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; RCT, randomised controlled trial; UDCA, ursodeoxycholic acid.

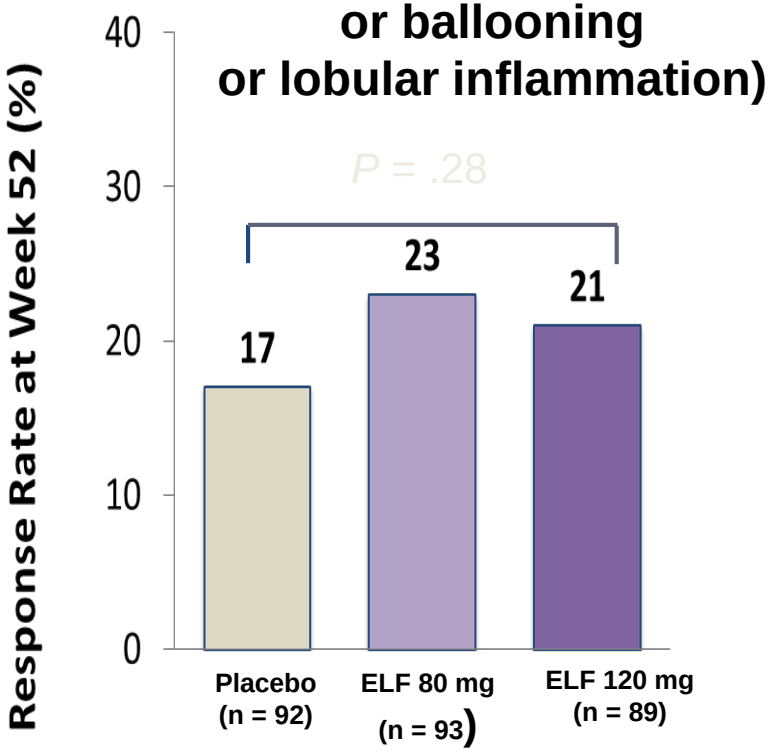
ClinicalTrials.gov. NCT01694849. https://clinicaltrials.gov/ct2/show/NCT01694849.

Ratziu V, et al. *Gastroenterology.* 2016 Feb 11. [Epub ahead of print]

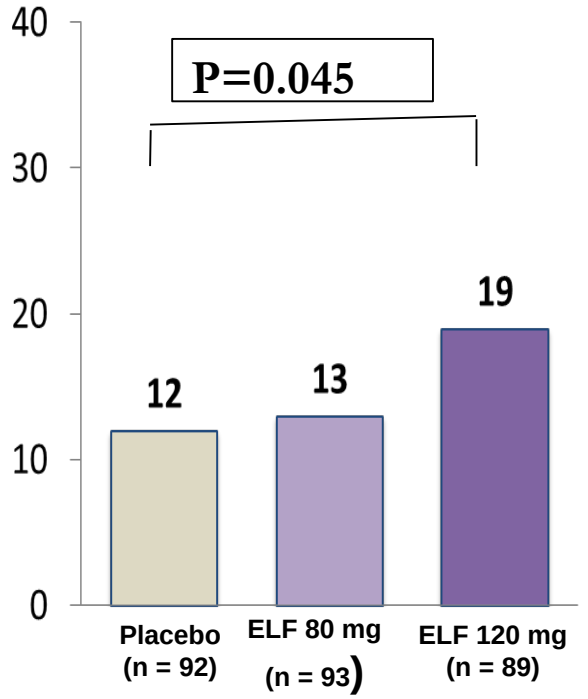
GOLDEN 505 Primary Endpoint in ITT Population

Resolution of NASH Without Fibrosis Worsening

Protocol-defined (disappearance of steatosis or ballooning or lobular inflammation)



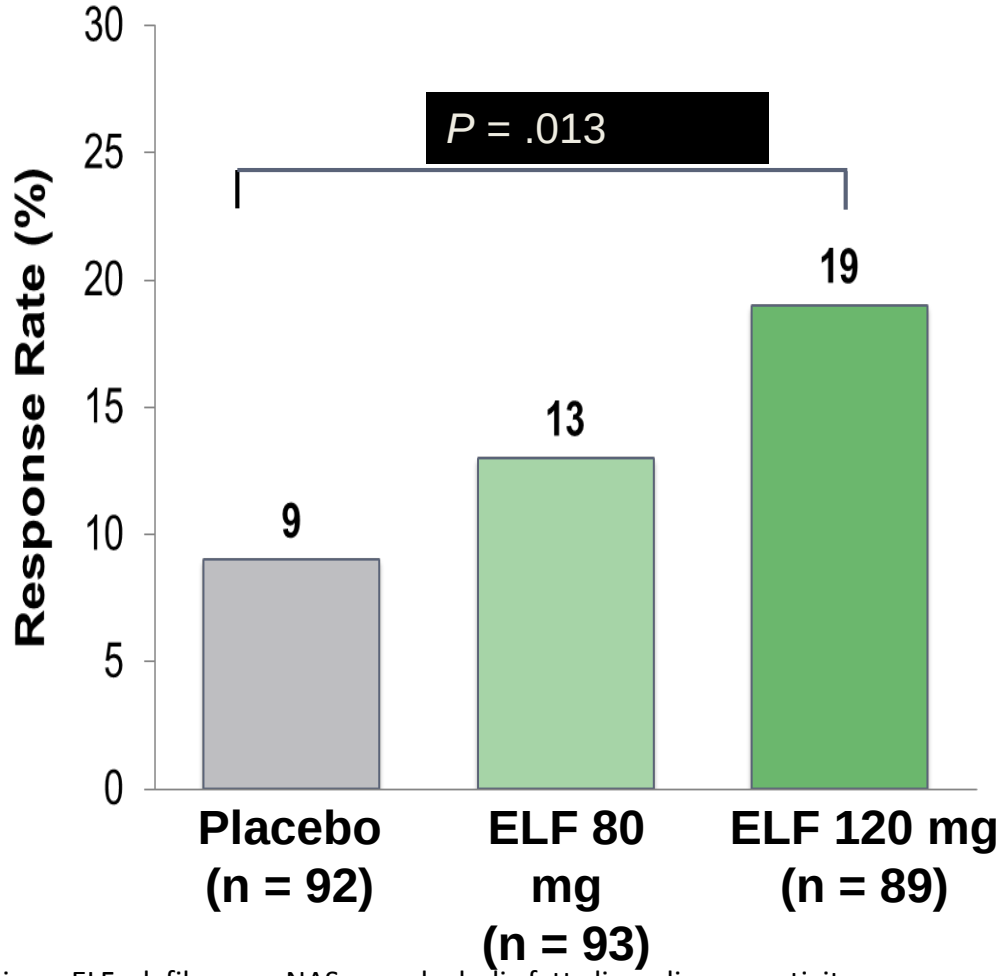
Modified definition (no ballooning; lobular inflammation none or mild)



Abbreviations: EASL, European Association for the Study of the Liver; ELF, elafibranor; ITT, intent-to-treat; NASH, nonalcoholic steatohepatitis. Ratziu V, et al. *Gastroenterology.* 2016 Feb 11. [Epub ahead of print]

Slide courtesy of Naga Chalasani (IU)

GOLDEN 505 Primary Endpoint in Patients with NAS ≥4 *Modified Definition*



Abbreviations: ELF, elafibranor; NAS, nonalcoholic fatty liver disease activity score.
Ratziu V, et al. *Gastroenterology.* 2016 Feb 11. [Epub ahead of print]

Slide courtesy of Naga Chalasani (IU)

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY, VOL. 67, NO. 5, 2018

A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of Nonalcoholic Steatohepatitis With Fibrosis

Scott L. Friedman,[1*] Vlad Ratziu,[2*] Stephen A. Harrison,[3] Manal F. Abdelmalek,[4] Guruprasad P. Aithal,[5] Juan Caballeria,[6] Sven Francque,[7] Geoffrey Farrell,[8] Kris V. Kowdley,[9] Antonio Craxi,[10] Krzysztof Simon,[11,12] Laurent Fischer,[13] Liza Melchor-Khan,[13] Jeffrey Vest,[14] Brian L. Wiens,[13] Pamela Vig,[13] Star Seyedkazemi,[13] Zachary Goodman,[15] Vincent Wai-Sun Wong,[16] Rohit Loomba,[17,18] Frank Tacke,[19] Arun Sanyal,[20**] and Eric Lefebvre[13**]

ILC 1368	**Cenicriviroc treatment for adults with non-alcoholic steatohepatitis: Year 2 analysis of the Phase 2b CENTAUR study** Ratziu C, et al. ILC 2018

Slide courtesy of Naga Chalasani (IU)

Cenicriviroc (CVC) Targets Inflammation & Fibrogenesis

NASH Disease Progression

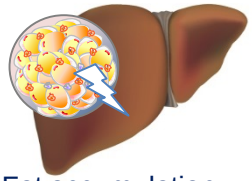
Metabolic-driven liver injury

⇩

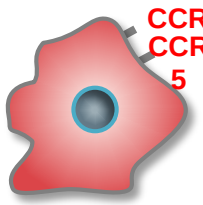
Evokes inflammatory response

⇩

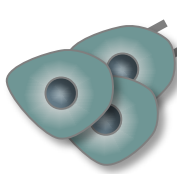
Drives fibrogenesis



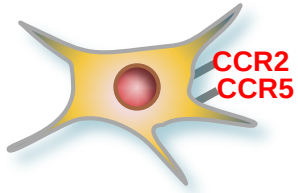
Fat accumulation drives liver injury



Kupffer Cell activation



Monocyte/macrophage recruitment



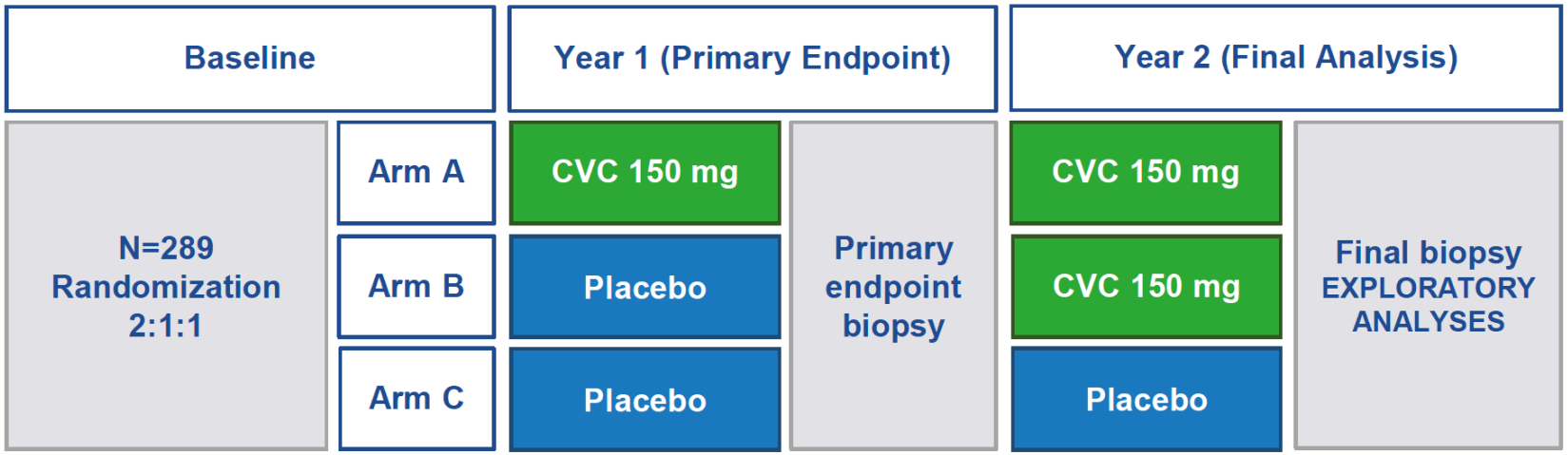
CVC Mechanism

- Block inflammatory signaling
- Disrupt fibrogenic signaling In activate stellate cells

- **Friedman, S. et al., Contemporary Clinical Trials, 47, March 2016**

CENTAUR Study Design

Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study

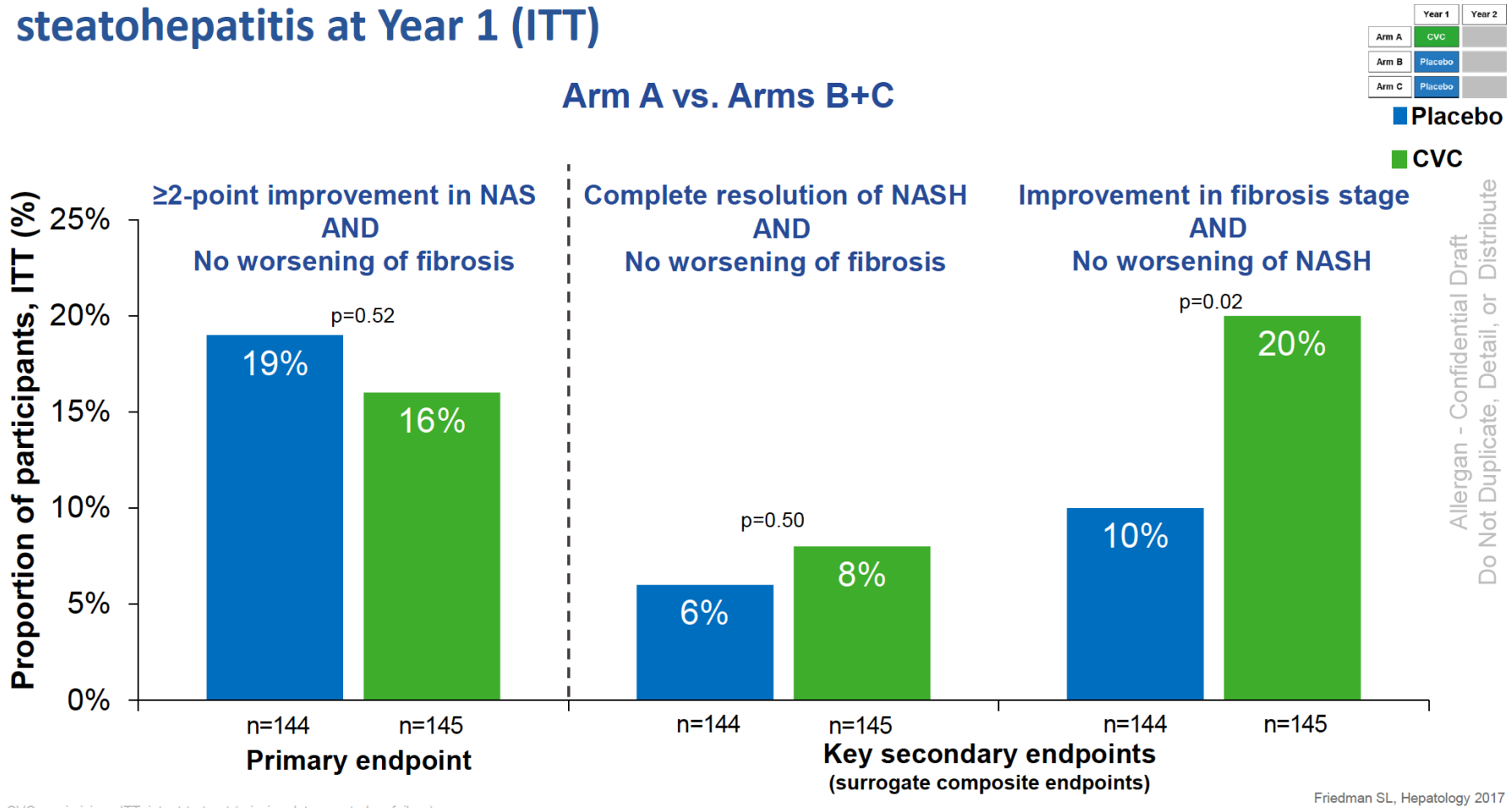


- First Phase 2b study in NASH to collect 3 serial biopsies over a 2-year duration
- Key eligibility criteria
  - Fibrosis stage 1-3 (NASH CRN), NASH diagnosis (NAS ≥4)
  - Enriched for T2DM, high BMI with at least 1 criteria of MetS, or bridging fibrosis and/or NAS ≥5
- Stratification factors: NAS (4 or ≥5) and fibrosis stage (≤2 or >2)
- Study conducted in the USA, EU, Australia, and Hong Kong

Slide courtesy of Naga Chalasani (IU)

CENTAUR Year 1 Results

CVC demonstrated antifibrotic effect without impact on underlying steatohepatitis at Year 1 (ITT)



CVC, cenicriviroc; ITT, intent-to-treat (missing data counted as failure);

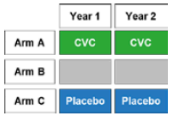
Friedman SL, Hepatology 2017
Wong V, APASL Annual Meeting 2017

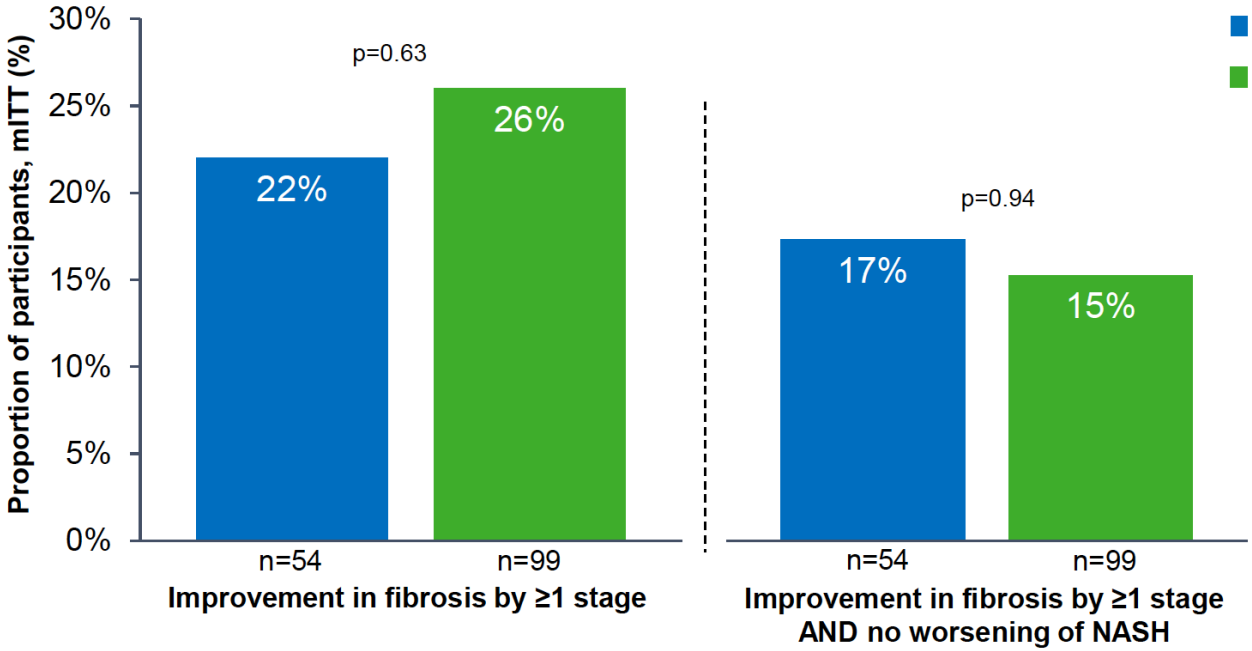
Slide courtesy of Naga Chalasani (IU)

Results

≥1-stage antifibrotic response with CVC following 2 years of treatment

Baseline to Year 2
Arm A vs. Arm C





Post-randomization biopsy at Year 2

	Placebo n (%)	CVC n (%)
Randomized	72	145
Evaluable	54 (75%)	99 (68.3%)
Non-evaluable	2 (2.8%)	4 (2.8%)
Missing*	16 (22.2%)	42 (29.0%)

Percentages based on randomized participants

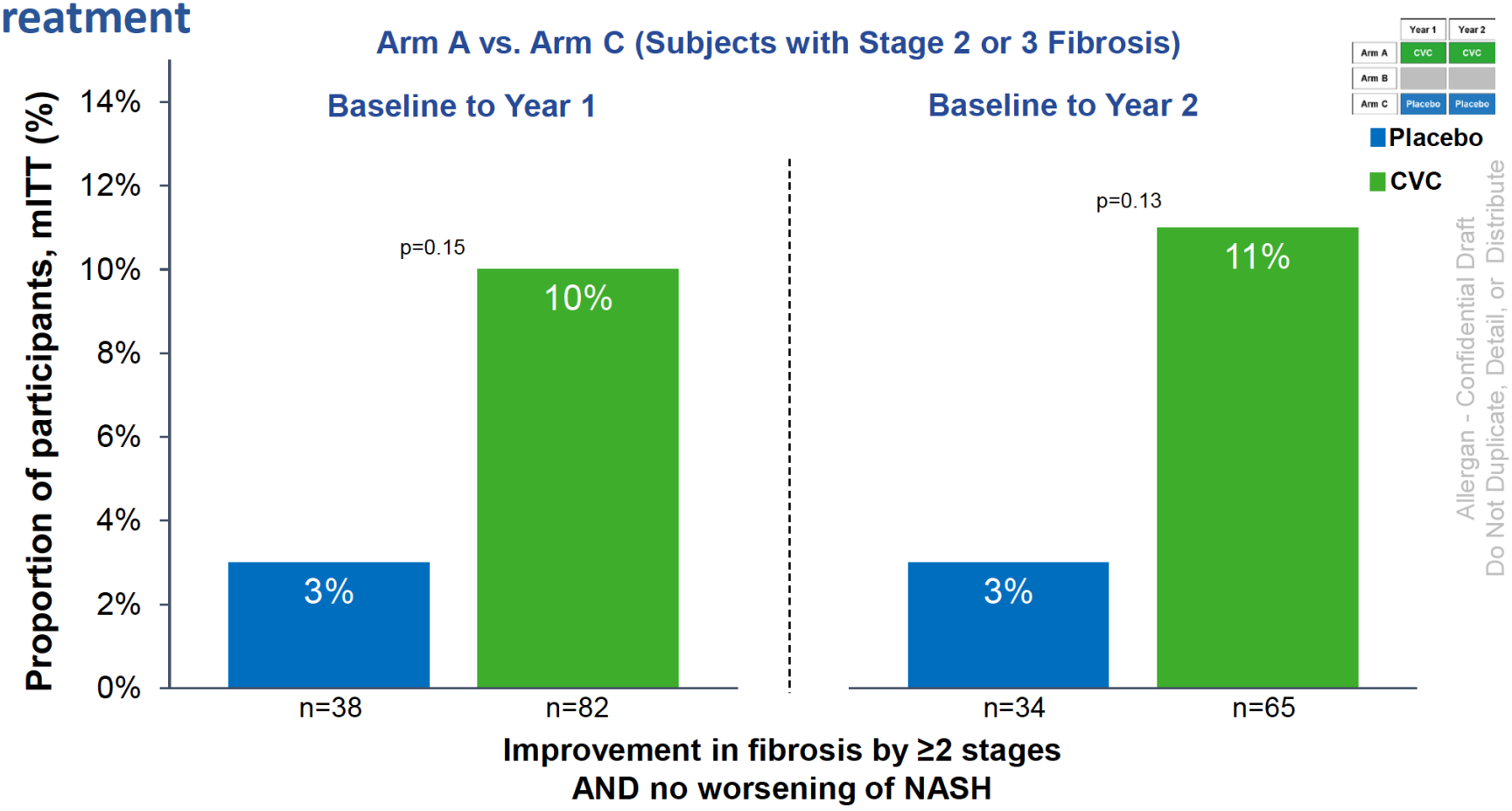
*Participants with missing post-Baseline biopsies were considered non-responders and excluded from the mITT analysis

*Imbalance in missing liver biopsies at Year 2 predominantly affected Arm A

Slide courtesy of Naga Chalasani (IU)

Results

≥2-stage antifibrotic response with CVC after 1 and 2 years of treatment



Slide courtesy of Naga Chalasani (IU)

HEPATOLOGY

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HEPATOLOGY, VOL. 67, NO. 2, 2018

The ASK1 Inhibitor Selonsertib in Patients With Nonalcoholic Steatohepatitis: A Randomized, Phase 2 Trial

Rohit Loomba,[1] Eric Lawitz,[2] Parvez S. Mantry,[3] Saumya Jayakumar,[4] Stephen H. Caldwell,[5] Hays Arnold,[6] Anna Mae Diehl,[7] C. Stephen Djedjos,[8] Ling Han,[8] Robert P. Myers,[8] G. Mani Subramanian,[8] John G. McHutchison,[8] Zachary D. Goodman,[9] Nezam H. Afdhal,[10] and Michael R. Charlton,[11] for the GS-US-384-1497 Investigators

Slide courtesy of Naga Chalasani (IU)

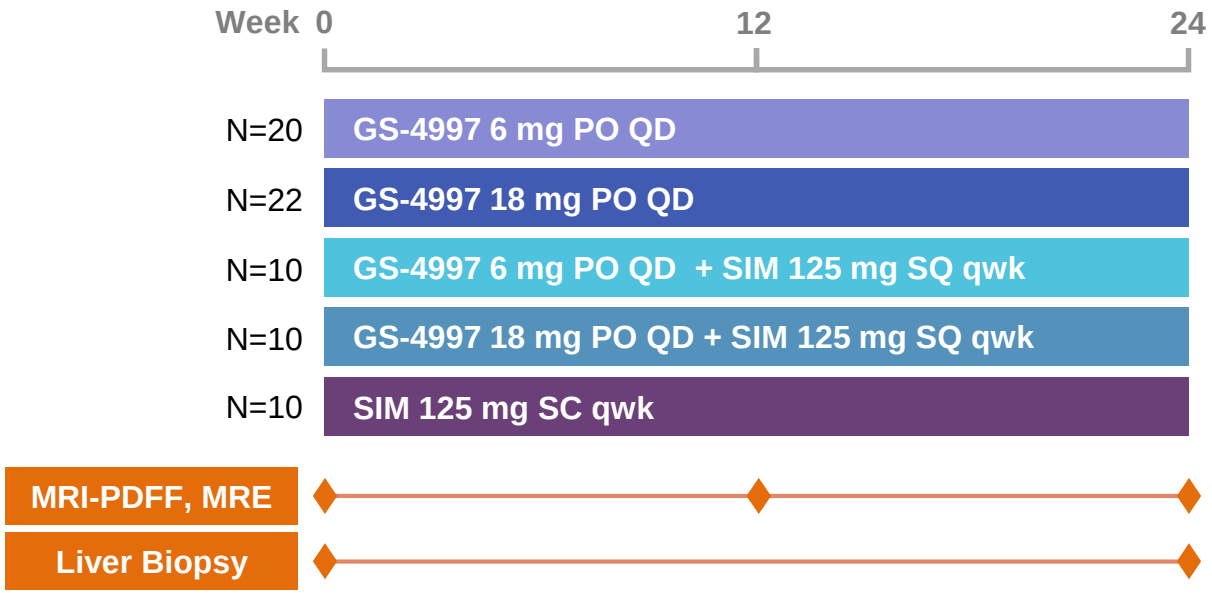
GS-4997, an Inhibitor of Apoptosis Signal-Regulating Kinase (ASK1), Alone or in Combination with Simtuzumab for the Treatment of Nonalcoholic Steatohepatitis (NASH): A Randomized, Phase 2 Trial

Rohit Loomba[1], Eric Lawitz[2], Parvez S. Mantry[3], Saumya Jayakumar[4], Stephen H. Caldwell[5], Hays Arnold[6], Anna Mae Diehl[7], C. Stephen Djedjos[8], Catherine Jia[8], Robert P. Myers[8], G. Mani Subramanian[8], John G. McHutchison[8], Zachary D. Goodman[9], Nezam H. Afdhal[10], Michael R. Charlton[11]

[1]University of California at San Diego, San Diego, CA; [2]Texas Liver Institute, San Antonio, TX; [3]The Liver Institute at Methodist Dallas, Dallas, TX; [4]University of Calgary, Calgary, AB, Canada; [5]University of Virginia, Charlottesville, VA; [6]Gastroenterology Consultants of San Antonio, San Antonio, TX; [7]Duke Clinical Research Institute, Durham, NC; [8]Gilead Sciences, Inc., Foster City, CA; [9]Inova Fairfax Hospital, Falls Church, VA; [10]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [11]Intermountain Medical Center, Salt Lake City, UT

AASLD 2016, Boston

Study Design



- Key inclusion criteria
  - Biopsy-proven NASH with NAS ≥5 (≥1 point for steatosis, lobular inflammation, hepatocellular ballooning)
  - F2–3 fibrosis
- 2:2:1:1:1 randomization (stratified by diabetes)

MRI-PDFF, magnetic resonance imaging-proton density fat fraction; MRE, magnetic resonance elastography; NAS, NAFLD Activity Score; SIM, simtuzumab.

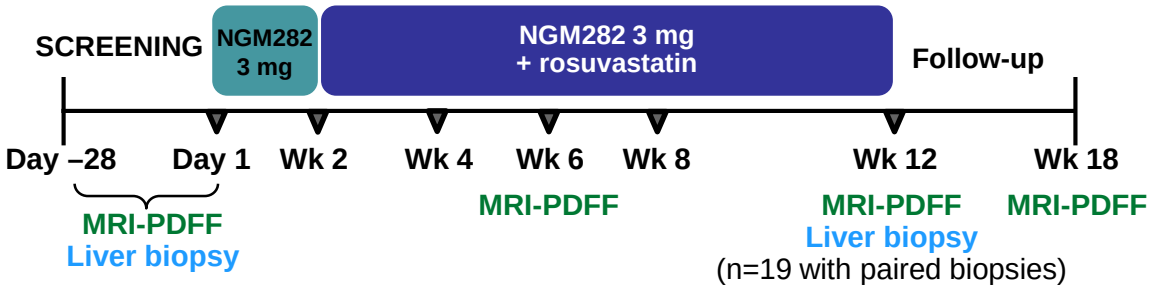
Selonsertib & NASH

- After 24 weeks of treatment in patients with NASH and F2–3 fibrosis, selonsertib at 18 mg/day has beneficial effects on:
  - Fibrosis regression and progression
  - Liver stiffness by MRE
  - MRI-PDFF
  - ALT and GGT
  - CK-18
- selonsertib was safe and well-tolerated
- Phase 3 trials of selonsertib in patients with NASH and advanced fibrosis and cirrhosis have been initiated.

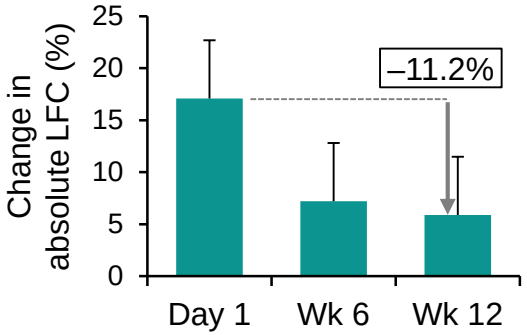
Slide courtesy of Naga Chalasani (IU)

NGM282 FGF19 analogue phase 2 trial

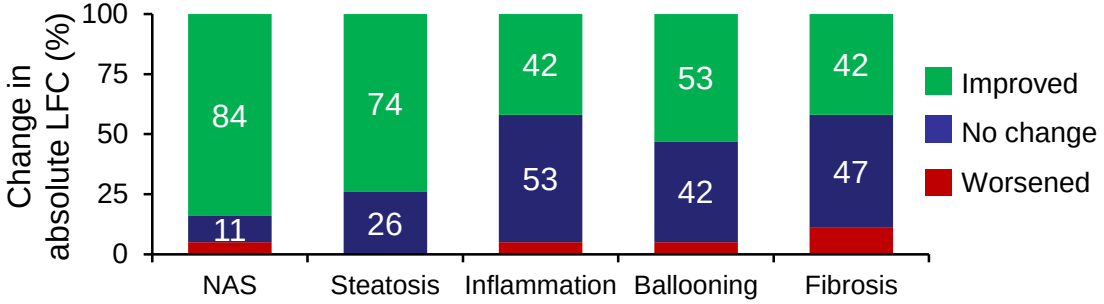
n=22 biopsy-confirmed NASH* patients



Change in absolute LFC at Week 12 (n=19)



12-week histology endpoints (n=19)



- **Primary endpoint:** 100% patients had decrease in absolute LFC ≥5%
- **Mean decrease in relative LFC was 67%;** 100% patients had relative LFC ≥30%
- Rapid and significant reductions in: (C4), ALT and AST, fibrosis markers (PRO-C3), and LIF

- **68% patients (n=13) were early histological responders**†
- **42% patients improved fibrosis ≥1 stage (3 patients F3→F1)**
- Elevations in LDL-C managed by rosuvastatin back to baseline or below target of 100 mg/dl
- **Safety and tolerability** favourable: most common AEs were mild loose/frequent stools and injection site reactions

Conclusions

- Unprecedented improvements in fibrosis and NASH-related histology, with earlier decreases in hepatic steatosis, liver transaminases and fibrosis markers

*NAS ≥4 (≥1 in each component), stage 1–3 fibrosis , absolute LFC ≥8% (MRI-PDFF)
†Defined as ≥1 stage fibrosis improvement, ≥2-point decrease in NAS or resolution of NASH
Harrison S, et al. ILC 2018, #5037 (GS-014)

Slide courtesy of Naga Chalasani (IU)

MGL-3196, a selective thyroid hormone receptor beta (THR-β) agonist: Phase 2 NASH study

Background

- MGL-3196 lowers LDL-C and TGs; and could reduce NASH by increased β-oxidation of liver lipids and improved mitochondrial function
- Safe and well tolerated in >300 dosed subjects (Phase 1)

Methods

- 125 patients with biopsy-proven NASH* and ≥10% liver fat on baseline MRI-PDFF randomized 2:1 to oral MGL-3196 qd or placebo for 36 weeks; blinded increase or decrease in dose possible based on exposure
- Serial liver biopsies performed

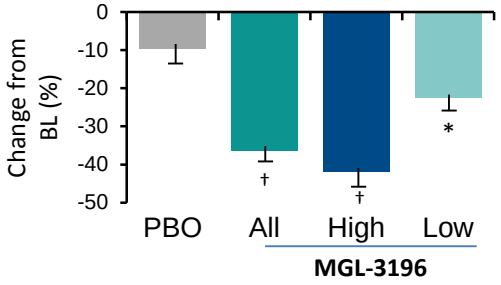
Results (Week 12)

- **Liver enzymes:** Decreases in ALT and AST in high-exposure MGL-3196 vs. PBO (p=0.04, 0.02, respectively)
- **Fibrosis biomarkers**: MGL-3196 significantly decreased ELF™ and Pro-C3 (up to 40% vs. PBO; p=0.009, 0.002, respectively) in patients with >ULN levels at baseline (reflective of more advanced fibrosis stage)
- **Safety**
  - Study still blinded; MGL-3196 shows very good tolerability: mostly mild–moderate AEs, balanced between all groups
  - Three SAEs, all unrelated to drug
  - No change in thyroid axis, heart rate or vital signs
  - Significant decreases in S/DBP for MGL-3196 vs. PBO

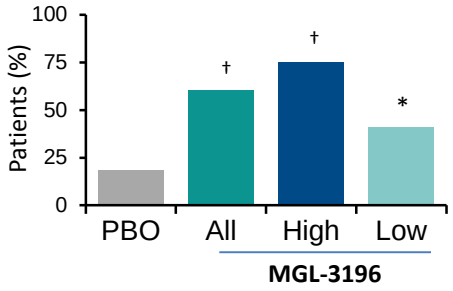
Conclusions

- MGL-3196 reduced NASH and liver fibrosis
- Histopathological assessment (36-week liver biopsy) will allow for correlations with baseline biopsy and multiple 12- and 36-week non-invasive imaging and biomarkers

- **Primary endpoint:** Relative change in liver fat on MRI-PDFF at 12 weeks

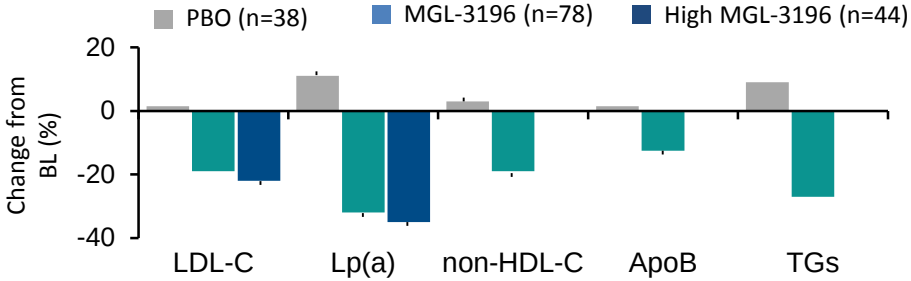


- Patients achieving ≥30% fat ↓

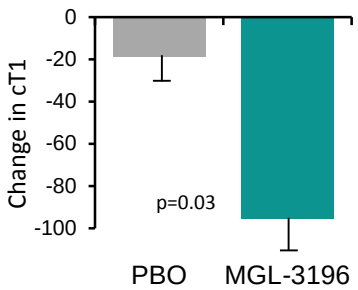


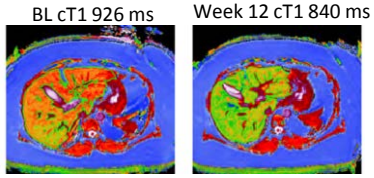
*p<0.05 vs PBO; †p<0.0001

- **Lipids:** meaningful reductions in atherogenic lipids (p<0.0001)



- **Multiparametric MRI-PDFF substudy:** Statistically sig. improvements in cT1 (shown to correlate with inflammation on liver biopsy)





MGL-3196-treated patient (nl cT1 826 ms)

*NAS ≥4, F1–3

Harrison A, et al. ILC 2018, #1977 (GS-009)

Slide courtesy of Naga Chalasani (IU)

MGL-3196, a selective thyroid hormone receptor beta (THR-β) agonist: Phase 2 NASH study

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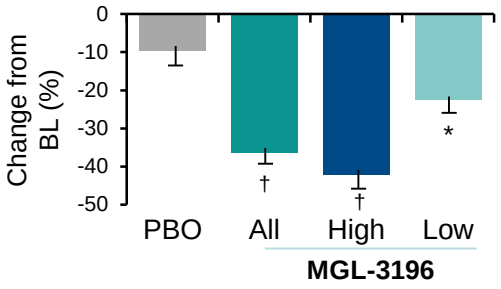
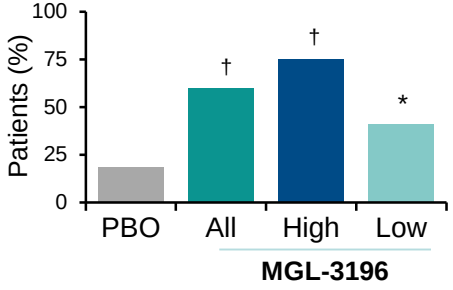
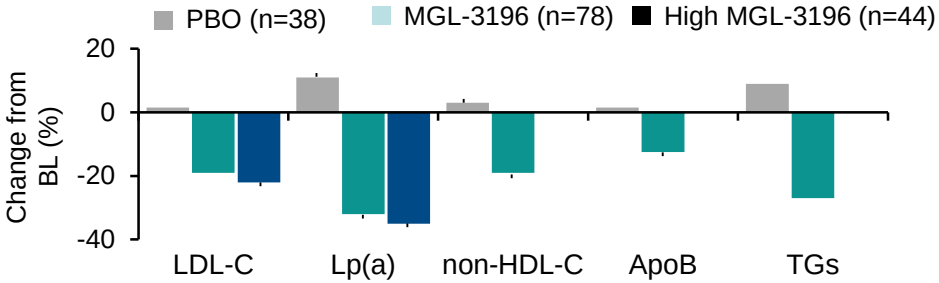
- **Primary endpoint:** Relative change in liver fat on MRI-PDFF at 12 weeks



- Patients achieving ≥30% fat ↓



- **Lipids:** meaningful reductions in atherogenic lipids (p<0.0001)



*NAS ≥4, F1–3

Harrison A, et al. ILC 2018, #1977 (GS-009)

Slide courtesy of Naga Chalasani (IU)

GR-MD-02, a Galectin-3 inhibitor, is better in patients with NASH cirrhosis without varices and mild portal hypertension (PH)

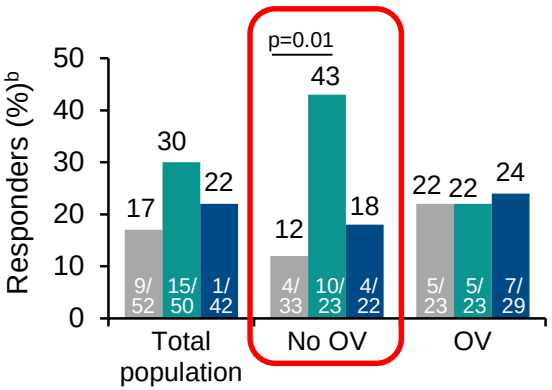
Background: Galectin-3 protein is implicated in the pathogenesis of NASH

Methods: 162 patients with NASH cirrhosis and PH, with no or small oesophageal varices (OVs), randomized 1:1:1 to 26 q2w IV infusions of GR-MD-02 2 mg/kg (GR2; n=54), 8 mg/kg (GR8; n=54), or PBO (n=54) over 52 weeks

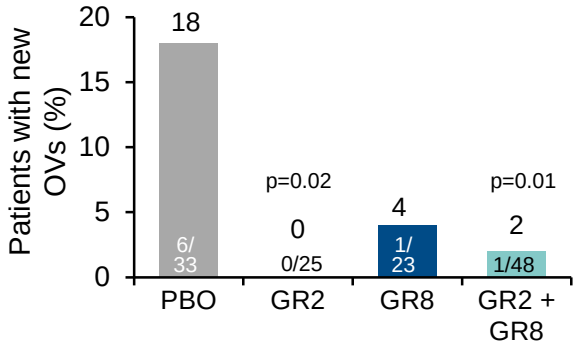
Results:

- No significant differences in **ΔHVPG** (primary endpoint), fibrosis, or NAS between PBO and GR in total population, only improvement in hepatocyte ballooning vs PBO with GR2 (p=0.03); trend with GR8 (p=0.08)
- **Mild PH subgroup**[a] (n=53; 20 PBO, 17 GR2, 16 GR8): Significant difference in ΔHVPG between PBO and GR8 (p=0.036)
- **Safety:** GR-MD-02 well tolerated; similar rate of AEs and SAEs. More patients discontinued GR8 due to AEs (n=5; PBO and GR2, n=0)

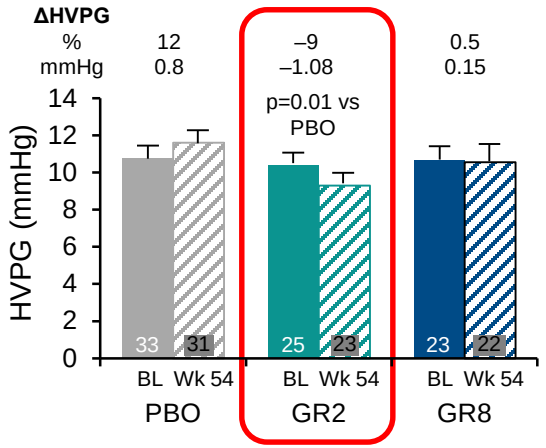
HVPG decrease greater in patients with no OV with GR2 but not GR8



Fewer GR-MD-02-treated patients developed new OVs at EOT



ΔHVPG in patients with no OVs at BL



Conclusions

- GR-MD-02 did not improve HVPG or liver fibrosis in total population, but significantly improved hepatocyte ballooning
- Significant and clinically relevant beneficial effects in **patients with NASH cirrhosis with no OV** and **mild PH** with GR2
- Significantly fewer GR2 patients developed new OVs at end-of-study
- These data warrant further investigating GR-MD-02 in NASH cirrhosis without varices

[a]HVPG between ≥6 and <10 mmHg at baseline; [b]HVPG decrease from baseline of both ≥2 mmHg and ≥20%

Chalasani N, et al. ILC 2018, #5569 (LBO-001)

Slide courtesy of Naga Chalasani (IU)

Summary

- Four drugs with different targets are in Phase 3 trials for NASH
  - Results expected in 1-2 years
- Many drugs in are Phase 2 trials with provocative results
- Future therapy may be combination therapy
- Ideally we will have personalized therapy
- Timeline: 2-5 years