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NASH Management: Agents in Late Stage Development

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Disclosures

Christina Hanson, FNP-C

Consultant: Salix, Clinical Area- HE, IBS-D

Speakers Bureau: AbbVie, Clinical Area- HCV

Speakers Bureau: Salix, Clinical Area- HE, IBS-D

Speakers Bureau: Intercept, Clincal Area- PBC

Learning Objectives

- Upon completion of this activity, participants should be able to:
  - Understand the current available treatment for NAFLD/NASH
  - Describe the mechanisms of action of novel agents in study for future treatment of NASH
  - Discuss recent evidence regarding the safety and efficacy of new and emerging agents for the treatment of NASH

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Current Treatment for NAFLD/NASH

Goals of NASH Treatment

- Improve metabolic abnormalities
- Decrease inflammation
- Prevent/arrest/reverse liver fibrosis
  - AASLD recommends pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis
- Prevent advanced liver disease, liver failure, liver cancer and related outcomes
- Systemic outcomes (eventually)

Chalasani N, et al. *Hepatology*. 2018;67:328-35.

Lifestyle Recommendations for Treating NASH

Caloric intake reduction

≥30% or ~750-1,000 kcal/day improved insulin resistance and hepatic steatosis

*Limit consumption of fructose-enriched beverages

Weight loss

of 3% to 5% can improve steatosis, but 6% to 10% is needed to improve NASH/fibrosis

Exercise

alone may reduce steatosis, but effect on other histologic features unknown

No heavy alcohol consumption

Insufficient data to guide recommendations regarding nonheavy alcohol consumption

**Drink ≥2 cups of caffeinated coffee daily

*Fructose increases the odds of the development of nonalcoholic fatty liver in high-risk patients and of nonalcoholic steatohepatitis and more advanced liver fibrosis in patients who already have nonalcoholic fatty liver disease.
**Caffeinated coffee reduces the risk of liver fibrosis in several liver diseases, including nonalcoholic fatty liver disease.
Chalasani N, et al. *Hepatology*. 2018;67(1):328-357; Diehl AM, Day C. *New Engl J Med.* 2017; 377:2063-72.

AASLD Practice Guidance: Vitamin E

- Vitamin E (800 IU/day)
  - May be considered for non-diabetic adults with biopsy-proven NASH (counsel patients on risks and benefits)
    - Improves liver histology, but not fibrosis
    - Long-term safety issues concerns linger (eg, impact on long-term mortality, prostate cancer)
- Vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
  - More data on safety and efficacy are needed

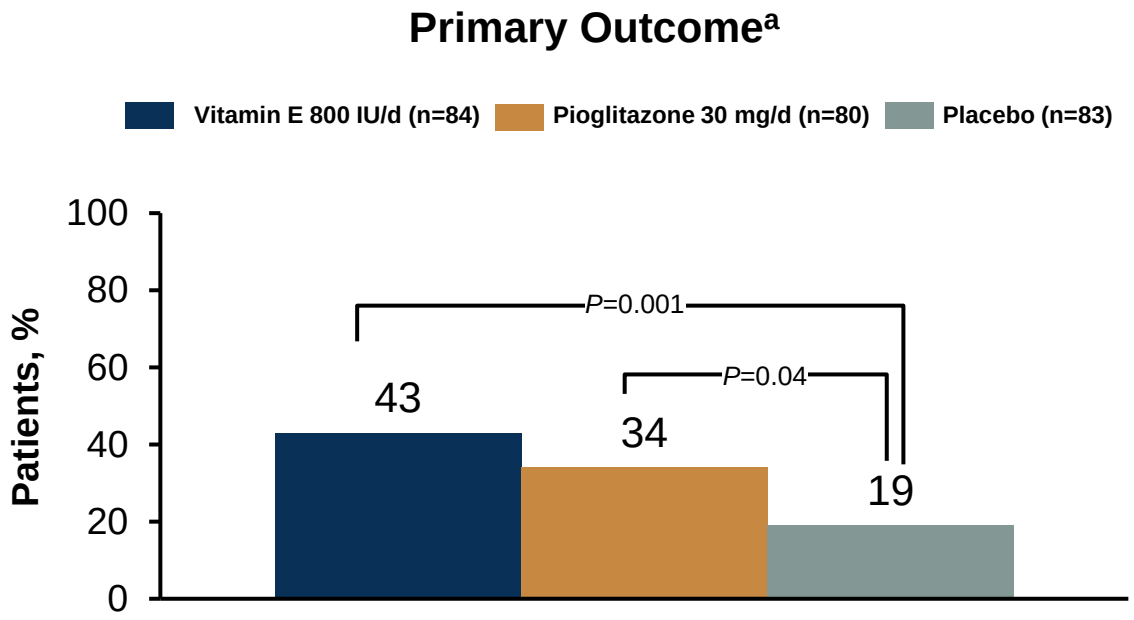
Chalasani N, et al. *Hepatology.* 2018;67:328-357.

AASLD Guidance for Use of Pioglitazone in NASH

- Improves liver histology in patients with and without T2DM and biopsy-proven NASH
  - May be used in treatment
- Should not be used in NAFLD without biopsy-proven NASH
- 2.5 to 4.7-kg weight increase in body weight with 12- to 36-month treatment
- Recent meta-analysis refutes concern about bladder cancer
- Bone loss may occur

Chalasani N, et al. *Hepatology*. 2018;67(1):328-357.

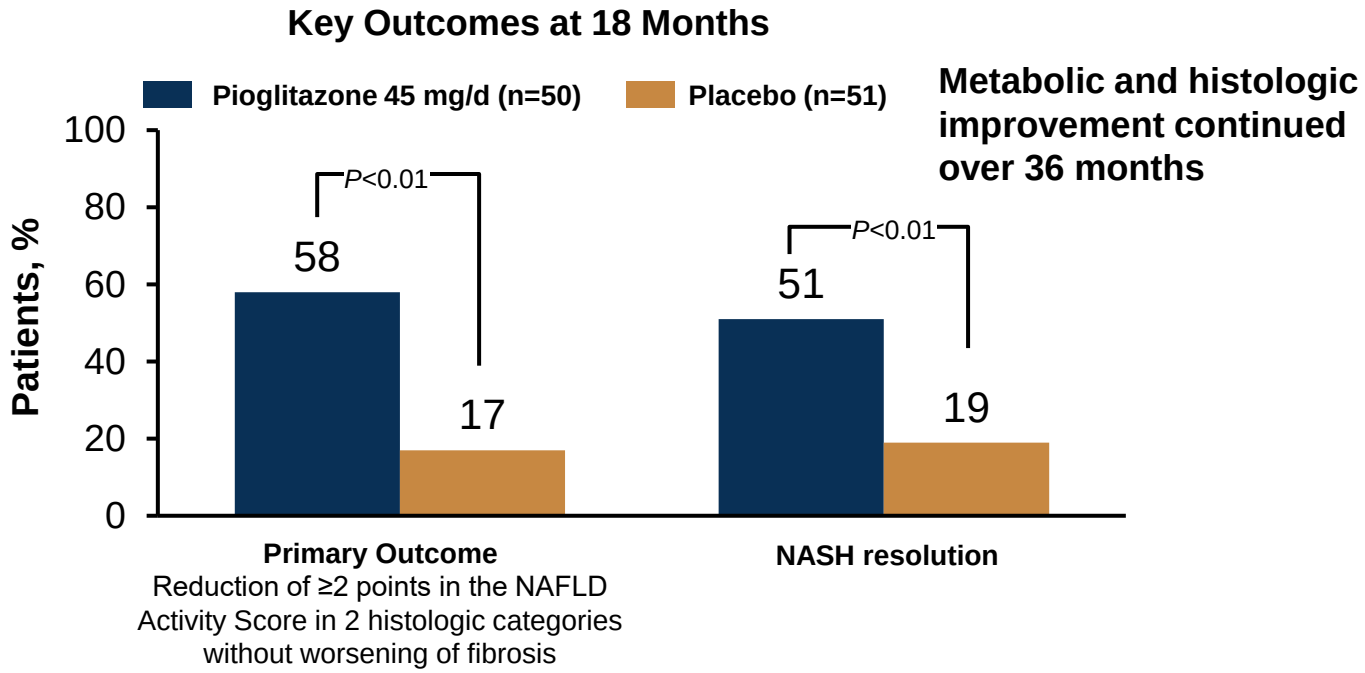
PIVENS Trial: Vitamin E or Pioglitazone for NASH



[a]Defined as NAS improvement by >2 points, including >1-point improvement in ballooning + 1-point improvement in either lobular inflammation or steatosis score + no increase in fibrosis.

Neuschwander-Tetri BA, et al. *Lancet*. 2015;385:956-965.

Pioglitazone for NASH in Patients With Prediabetes or T2DM



Cusi K, et al. *Ann Intern Med*. 2016;165:304-315.

AASLD Guidance for Managing CVD and Dyslipidemia

- Patients with NAFLD are at high risk for cardiovascular morbidity and mortality
  - Aggressive modification of CVD risk factors should be considered in all patients with NAFLD
- Statins can be used to treat dyslipidemia in patients with NAFLD and NASH
  - Statins may be used in patients with NASH cirrhosis, but should be avoided in patients with decompensated cirrhosis

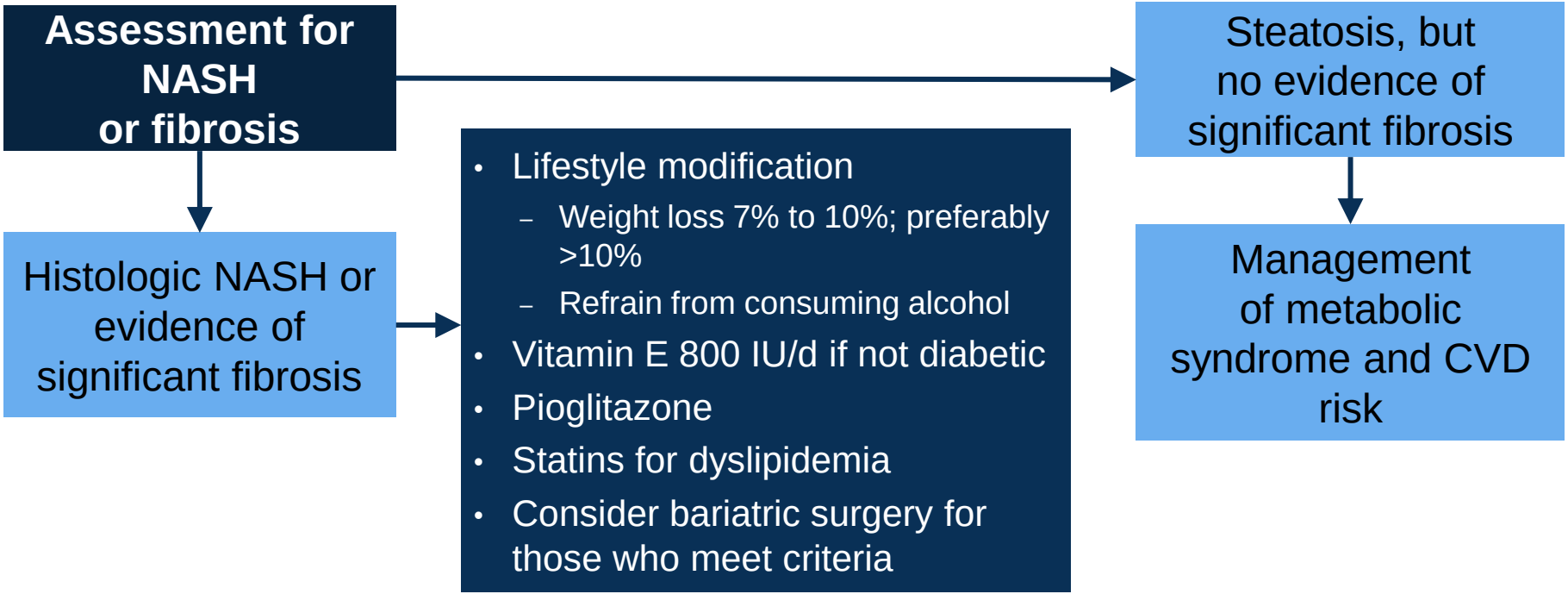
Chalasani N, et al. *Hepatology*. 2018;67(1):328-357.

Treatments Not Currently Recommended for NASH

Therapy	Comments
Metformin	• Does not improve liver histology despite reducing ALT and insulin resistance
GLP-1 agonists	• Trial of liraglutide showed resolution of NASH, less fibrosis progression, weight loss • Further trials expected
UDCA	• Histologic benefit not shown
Omega-3 fatty acids	• No proven benefit in NASH • Can be used for hypertriglyceridemia
Obeticholic acid	• Phase 3 trials at higher dose than for PBC
Probiotics	

Chalsani N, et al. *Hepatology*. 2017 Jul 17. [Epub ahead of print];
Paolella G, et al. *World J Gastroenterol*. 2014;20:15518-15531.

Summary: Current Treatments for NASH



Chalasani N, et al. *Hepatology.* 2018;67:328-357.

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Emerging Treatment Options for NAFLD/NASH

NASH Clinical Trial Endpoints in Early Phase III Development: Liver Histologic Improvement

NASH Resolution

- **Resolution of steatohepatitis on overall histopathologic reading**

and

- **No worsening of liver fibrosis**

Fibrosis Improvement

- **Improvement ≥ 1 fibrosis stage**

and

- **No worsening of steatohepatitis**

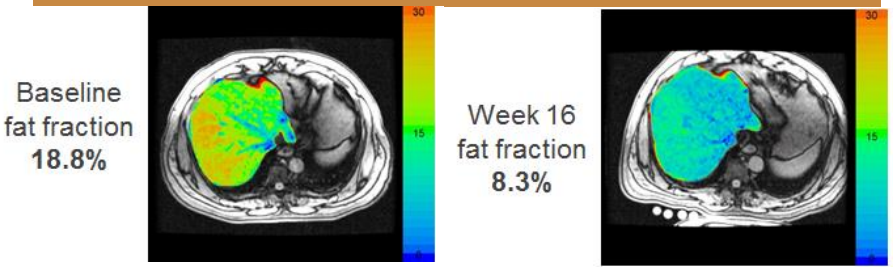
1. US FDA. Draft Guidance. Noncirrhotic NASH With Liver Fibrosis. December 2018.

NASH Clinical Trial Endpoints in Early Phase II Development

ALT

10 U/L reduction associated with histologic improvement or resolution of NASH[1]

≥ 17 U/L reduction predicts histologic response[2]



Liver Fat Fraction (MRI-PDFF)

≥ 5% absolute reduction associated with improvement in steatosis[3]

≥ 30% relative reduction associated with improvement in NAFLD activity score without fibrosis worsening[4]

- In large clinical trials that include paired biopsies, surrogate endpoints can be validated against histologic endpoints

Slide credit: clinicaloptions.com.

1. Vuppalanchi. *Clin Gastroenterol Hepatol*. 2014;12:2121; 2. Loomba. *Gastroenterology*. 2019;156:88;
3. Middleton. *Gastroenterology*. 2017;153:753; 4. Patel. *Therap Adv Gastro.* 2016;9:692.

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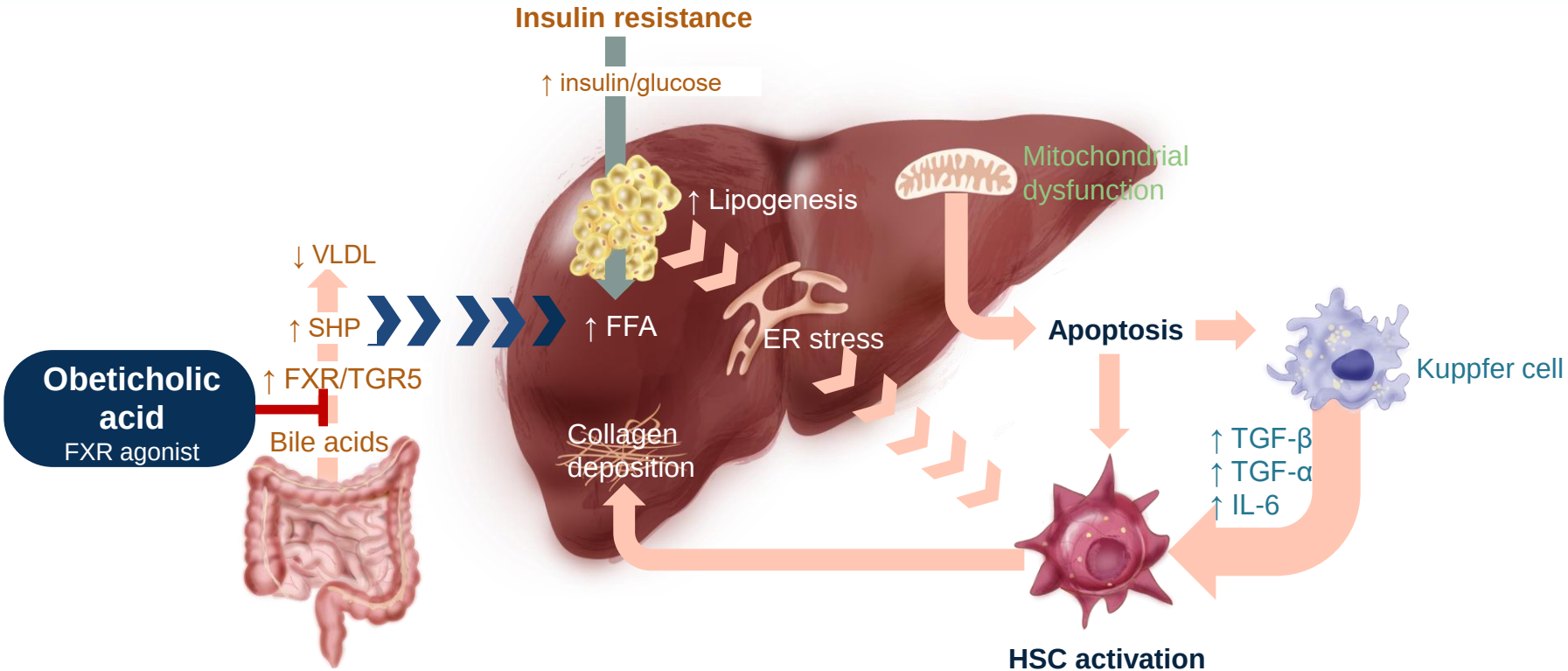
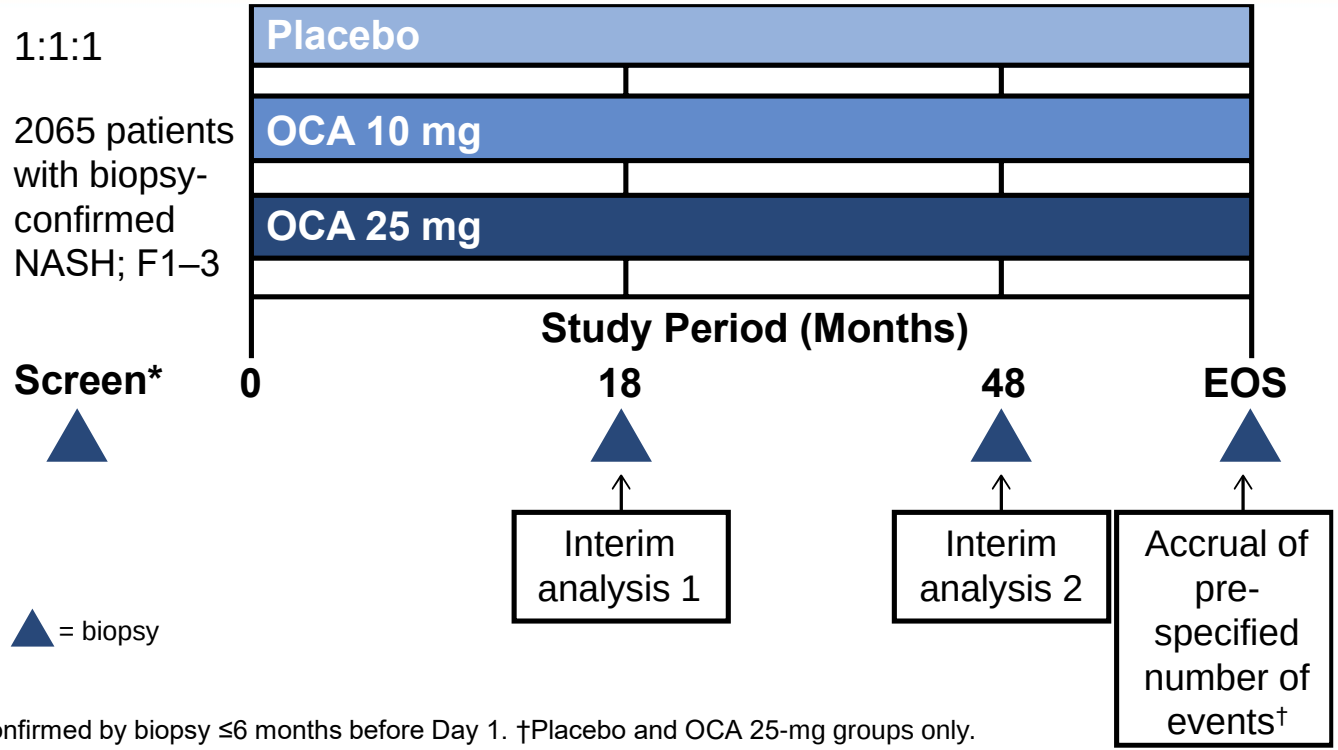
Gut-Liver Axis/Bile Acids

Mechanisms of Late-Stage Investigational Agents for NASH: Obeticholic Acid



ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
Adapted from Konerman MA et al. *J Hepatol*. 2018;68:362-365.

The REGENERATE Study



*NASH confirmed by biopsy ≤6 months before Day 1. †Placebo and OCA 25-mg groups only.
Abbreviations: EOS, end of study; OCA, obeticholic acid.

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02548351.
Ratziu V, et al. Abstract THU-488. Presented at: EASL 2016; 13-17 April, 2016; Barcelona, Spain.

Obeticholic Acid*: The REGENERATE Study

Fibrosis improvement at Month 18	Placebo	OCA 10 mg	OCA 25 mg
ITT Population: NASH with stage 2 or 3 Fibrosis	N= 311	N= 312	N= 308
Fibrosis Improvement (≥1 stage) with no worsening of NASH	11.9%	17.6% p=0.0446	23.1% p=0.0002
Fibrosis Improvement >2 stages) with no worsening of NASH	4.5	7.1	13.3
NASH resolution without worsening of fibrosis	8	11.2	11.7

- "In the primary efficacy analysis, once-daily OCA 25 mg met the primary endpoint of fibrosis improvement (≥1 stage) with no worsening of NASH at the planned 18-month interim analysis (p=0.0002 vs. placebo)"
- Phase 3 study in NASH patients with stage 2 and 3 fibrosis

* Under FDA review

Younossi ZM, et al. *Lancet*. 2019;394:2184-2196.

REGENERATE (Phase III Trial) for Obeticholic Acid18 Months Results (Feb 19, 2019)

Primary efficacy endpoints (ITT patients with stage 2,3 fibrosis)	Placebo (n=311)	OCA 10 mg (n= 312)	OCA 25 mg (n=308)
Fibrosis improvement ≥ 1 stage with no worsening of NASH*	11.9%	17.6% (p=0.0446)	23.1% (p=0.0002)
NASH resolution with no worsening of fibrosis	8.0%	11.2% (p=0.1814)	11.7% (p=0.1268)
Additional full efficacy (ITT patients + patients with stage 1 fibrosis at risk for progression)	**Placebo (n=407)**	**OCA 10 mg (n=407)**	**OCA 25 mg (n=404)**
Fibrosis improvement ≥ 1 stage with no worsening of NASH*	10.6%	15.7% (p=0.0286)	21.0% (p<0.0001)
NASH resolution with no worsening of fibrosis	7.9%	11.3% (p=0.0903)	14.9% (p=0.0013)

*Defined as no worsening of hepatocellular ballooning, no worsening of lobular inflammation and no worsening of steatosis.

The REGENERATE Study: Safety

- The frequency of serious AEs was similar across treatment groups (11–14%)
- No single serious adverse event occurred in more than 1% of patients in any treatment group
- The most frequent adverse event was pruritus

	Placebo (n = 657)	Obeticholic acid 10 mg (n = 653)	Obeticholic acid 25 mg (n = 658)
Treatment-emergent and serious adverse events			
At least one treatment-emergent adverse event	548 (83%)	579 (89%)	601 (91%)
Severity*			
Mild	160 (24%)	163 (25%)	130 (20%)
Moderate	294 (45%)	323 (49%)	338 (51%)
Severe	87 (13%)	89 (14%)	130 (20%)
Life-threatening	5 (1%)	4 (1%)	2 (< 1%)
Death	2 (< 1%)	0	1 (< 1%)
Leading to treatment discontinuation	41 (6%)	39 (6%)	83 (13%)
Serious adverse events	75 (11%)	72 (11%)	93 (14%)
Adverse events in ≥ 5% of patients in either obeticholic acid group			
Skin and subcutaneous tissue disorders			
Pruritus	123 (19%)	183 (28%)	336 (51%)
Grade 1 (mild of localized)	90 (14%)	113 (17%)	148 (22%)
Grade 2 (intense or widespread)	30 (5%)	67 (10%)	152 (23%)
Grade 3 (Intense or widespread and limit activities of daily living)	3 (< 1%)	3 (< 1%)	36 (5%)

Younossi ZM, et al. *Lancet*. 2019;394:2184-2196.

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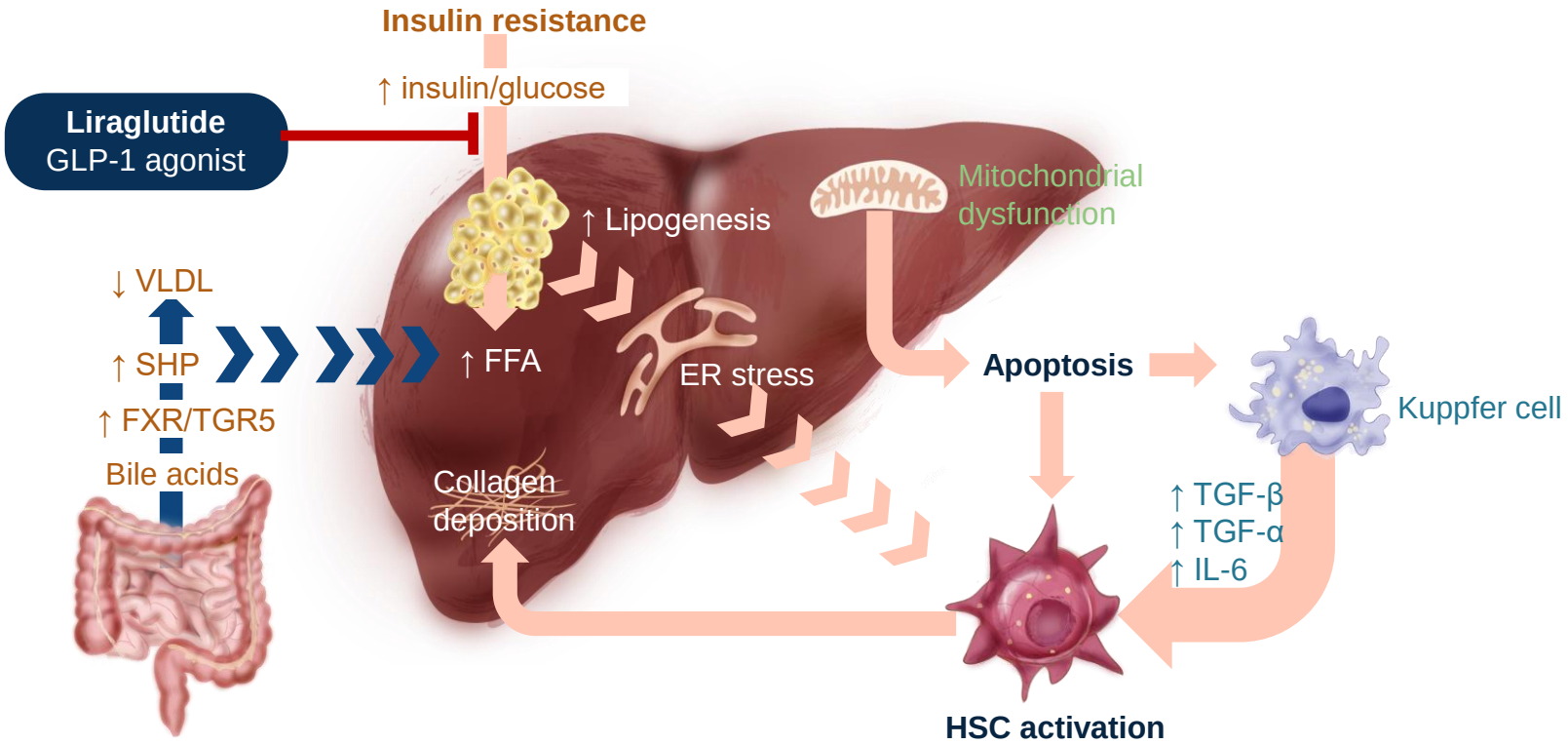
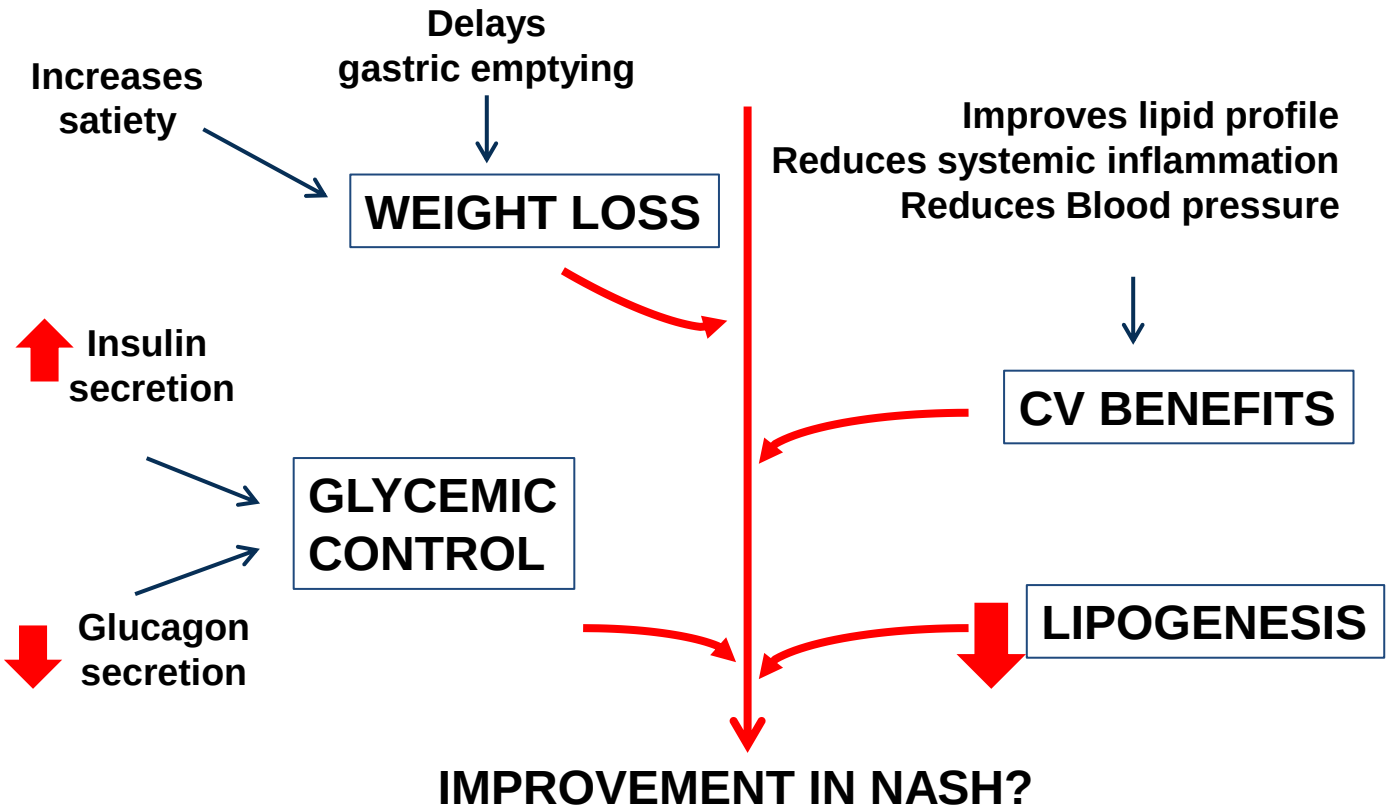
Inflammation/Fibrosis Targets

Mechanisms of Late-Stage Investigational Agents for NASH: Liraglutide

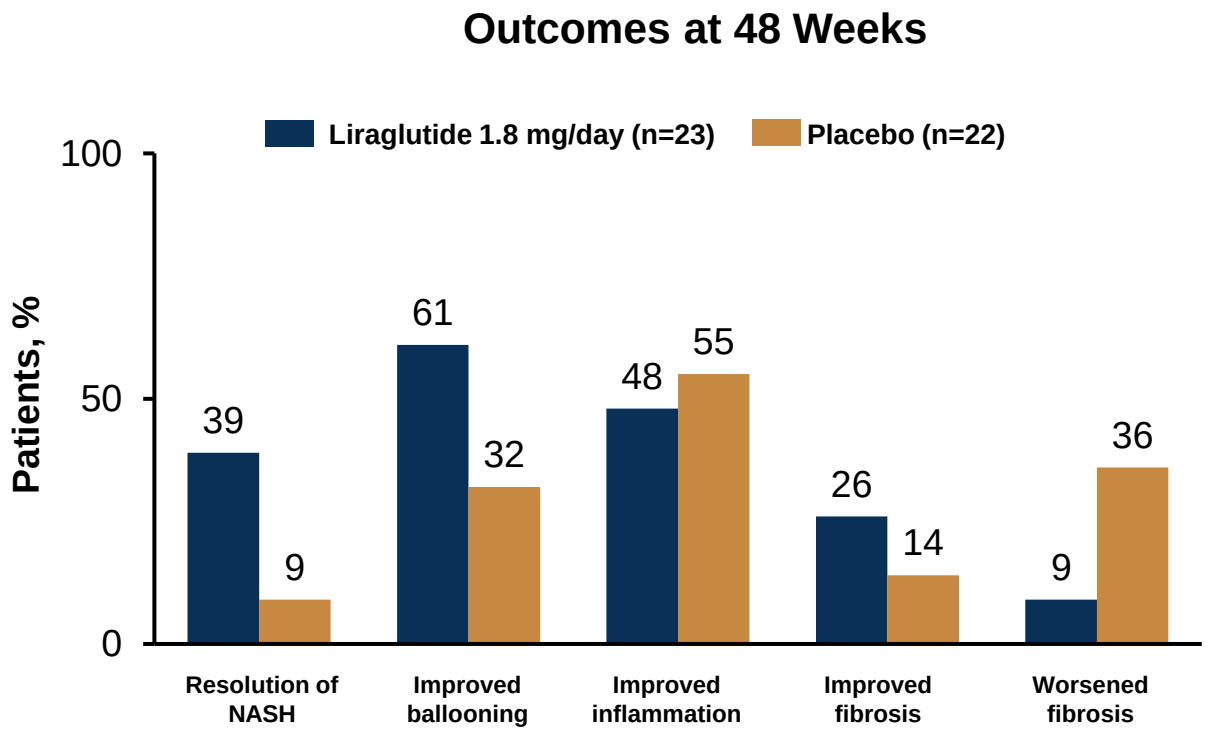


ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
Adapted from Konerman MA, et al. *J Hepatol*. 2018;68:362-365.

Multifactorial Effects of GLP1RA



Liraglutide in Overweight Patients With NASH: LEAN Study



Armstrong MJ, et al. *Lancet*. 2016;387:679-690.

Safety of Liraglutide in Patients With Diabetes

Event	Liraglutide 1.2 mg n= 645	Liraglutide 1.8 mg n= 1024	Placebo n= 661
	%		
Nausea	18	20	5
Diarrhea	10	12	4
Headache	11	10	7
Nasopharyngitis	9	10	8
Vomiting	6	9	2
Decreased appetite	10	9	1
Dyspepsia	4	7	1
Upper respiratory tract infection	7	6	6
Constipation	5	5	1
Back pain	4	5	3

Adverse Reactions Reported in ≥5%[a] of Liraglutide-treated Patients with Diabetes

[a]Excluding hypoglycemia.

Liraglutide (Victoza) [prescribing information]. Plainsboro, NJ; Novo Nordisk, Inc.; 2017.

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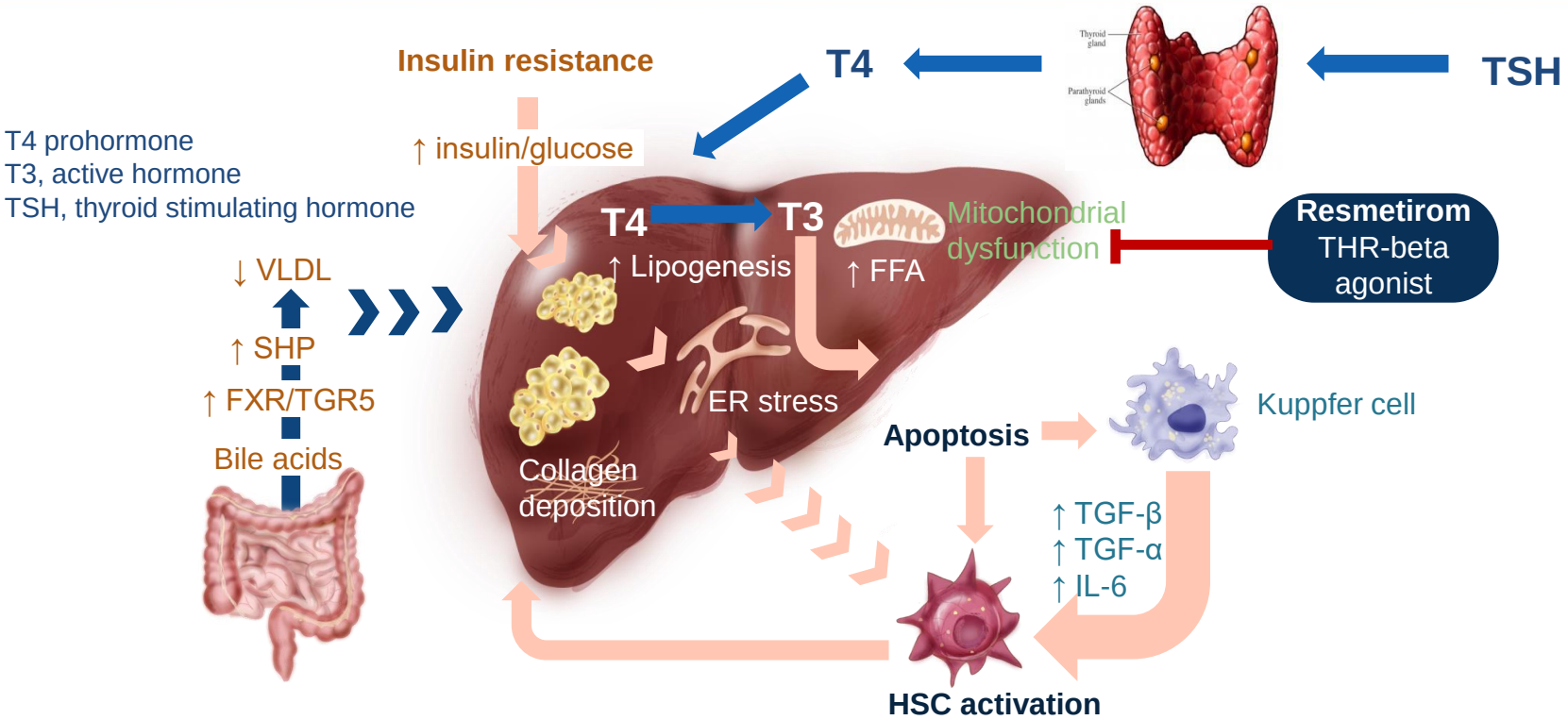
Metabolic Targets

Mechanisms of Late-Stage Investigational Agents for NASH: Resmetirom

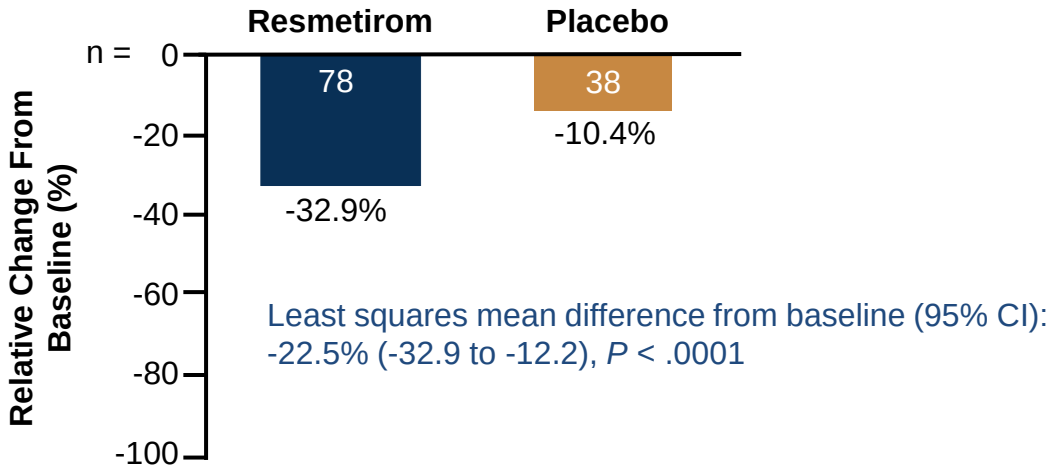


ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
Adapted from Konerman MA, et al. *J Hepatol*. 2018;68:362-365.

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



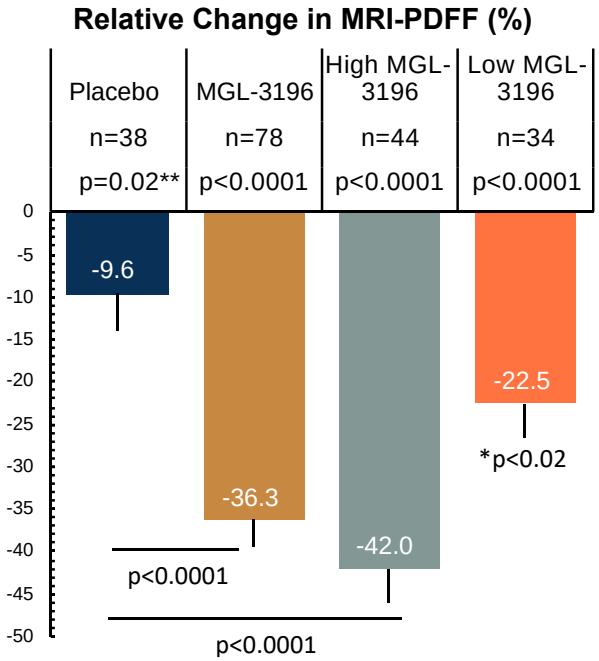
Least squares mean difference from baseline (95% CI): -22.5% (-32.9 to -12.2), *P* < .0001

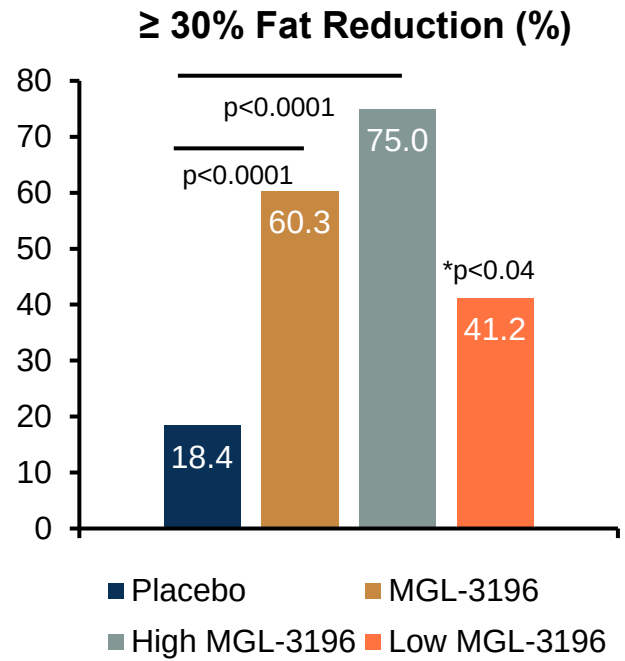
Slide credit: clinicaloptions.com

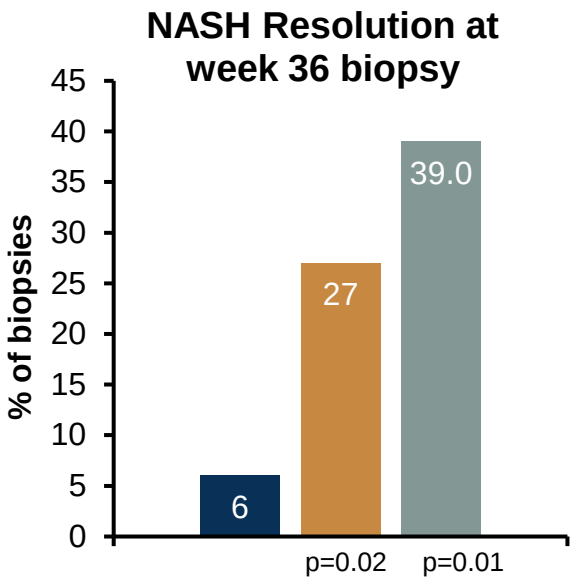
Harrison. *Lancet*. 2019 [Epub].

Resmetirom Significantly Decreases Hepatic Fat in NASH Patients at Week 12 MRI-PDFF, and Was Associated With NASH Resolution at Week 36 Biopsy

Fat Reduction at week 12 MRI-PDFF







Harrison SA, et al. *J Hepatol.* 2019;70(suppl):e791-e792. Abstract SAT-347.

Safety of Resmetirom

	Main study (36wk) Placebo N=42	Extension (36wk) Resmetirom N=31
Patients with AE's n (%)	**28 (68)**	**18 (58)**
Severe	2 (5)	0
Moderate	13 (32)	10 (32)
Mild	13 (32)	8 (27)
Patient with SAE's	2 (5)	0
Most common AE's n (%)		
Diarrhea	4 (10)	3 (10)
Nausea	2 (5)	1 (3)
Headache	6 (15)	0
UTI	4 (10)	1 (3)
Dizziness	4 (10)	1 (3)
Grade 3 CTC		
ALT>5xULN	3 (7)	
GGT>5xULN	5 (12)	0

Harrison Stephen, et al. "EFFECTS OF RESMETIROM (MGL3196) ON HEPATIC FAT, LIPIDS, LIVER ENZYMES AND MARKERS OF LIVER FIBROSIS IN AN OPEN LABEL 36 WEEK EXTENSION STUDY IN NASH PATIENTS". https://www.madrigalpharma.com/newsroom/nash-experts-webcasts/

Conclusions

- Patients with histologic NASH or evidence of significant fibrosis should be treated according to AASLD guidelines
- Many potential mechanisms in NASH represent disease-specific therapeutic targets
  - Multiple trials targeting a wide array of potential NASH pathogenic pathways are underway
  - Combination therapies with different targets may provide a synergistic histopathologic benefit
- Combination therapy using drugs with different mechanisms of action is likely the future of NASH treatment