Phase 3 development of resmetirom, a liver-directed thyroid hormone receptor (THR)-β agonist for the treatment of patients with NASH and significant liver fibrosis

Madrigal Satellite Symposium

ILC 2021

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Phase 3 development of resmetirom, a liver-directed thyroid hormone receptor (THR)-β agonist for the treatment of patients with NASH and significant liver fibrosis

Madrigal Satellite Symposium agenda

Time	Topic	Speaker
	Welcome and introduction	Stephen Harrison
	The contribution of metabolic co-morbidities and hepatic thyroid hormone dysregulation to the pathophysiology of NASH	Vlad Ratziu
	The utilization of non-invasive technologies for the identification of NASH patients and monitoring of treatment response in the clinical setting	Jörn Schattenberg
	Resmetirom as a treatment for NASH: Updates from the MAESTRO Phase 3 clinical trials	Stephen Harrison
	Conclusion and final discussion	All

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The contribution of metabolic co-morbidities and hepatic thyroid hormone dysregulation to the pathophysiology of NASH

Vlad Ratziu

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Disclosures

- Astra-Zeneca, Boehringer-Ingelheim, Galmed, Genfit, Madrigal, Poxel, Terns, Theratechnologies, Intercept, Inventiva, Novo-Nordisk, Bristol-Myers-Squibb, Hanmi
- Grant support: Gilead Sciences

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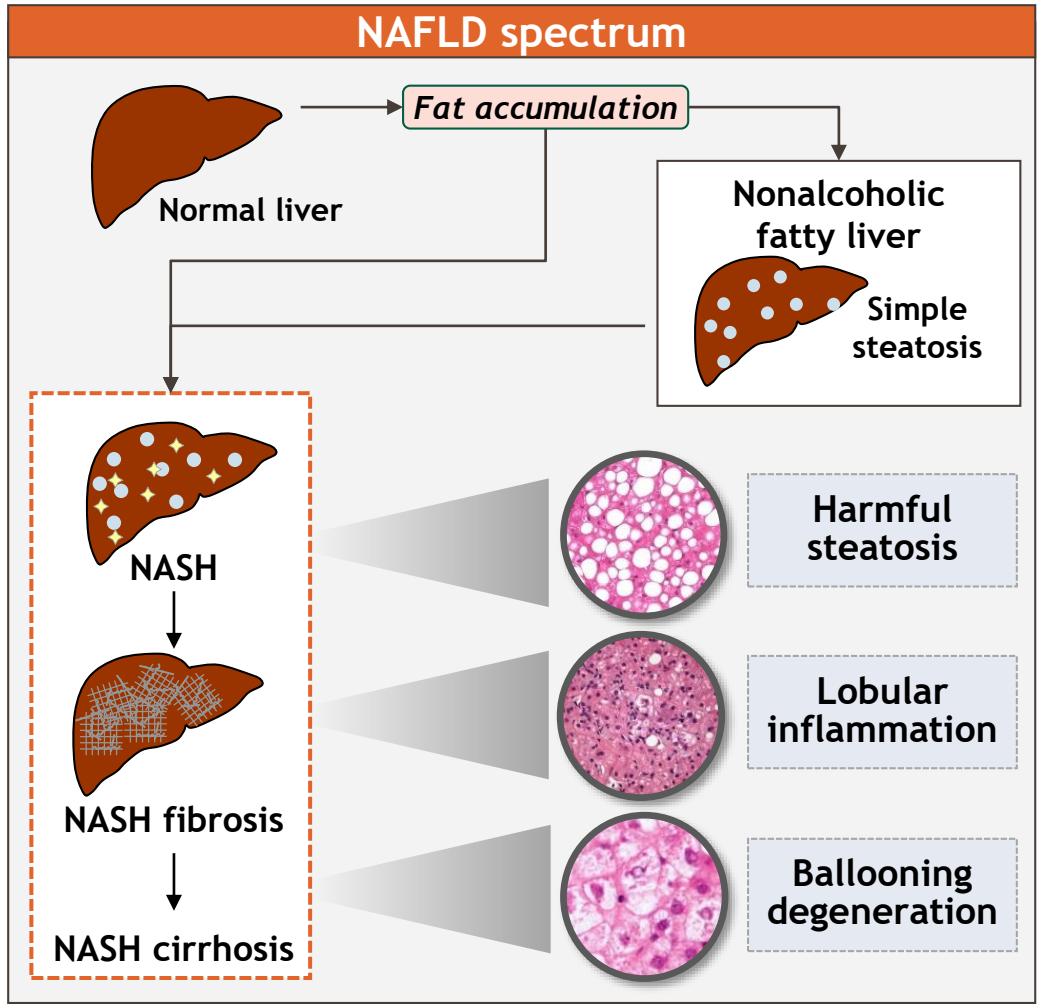
NAFLD ranges from simple steatosis (NAFL) to NASH

NAFLD = Non-alcoholic fatty liver disease

- NAFL: Non-alcoholic fatty liver
  - >5% of fat in the liver.
- NASH: Non-alcoholic steatohepatitis
  - Steatosis + ballooning + inflammation
- NASH with fibrosis
  - Mild, fibrosis stage 1
  - Significant, fibrosis stage 2 and 3
  - Cirrhosis, fibrosis stage 4



NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.
Sheka et al. JAMA. 2020;323(12):1175-1183.

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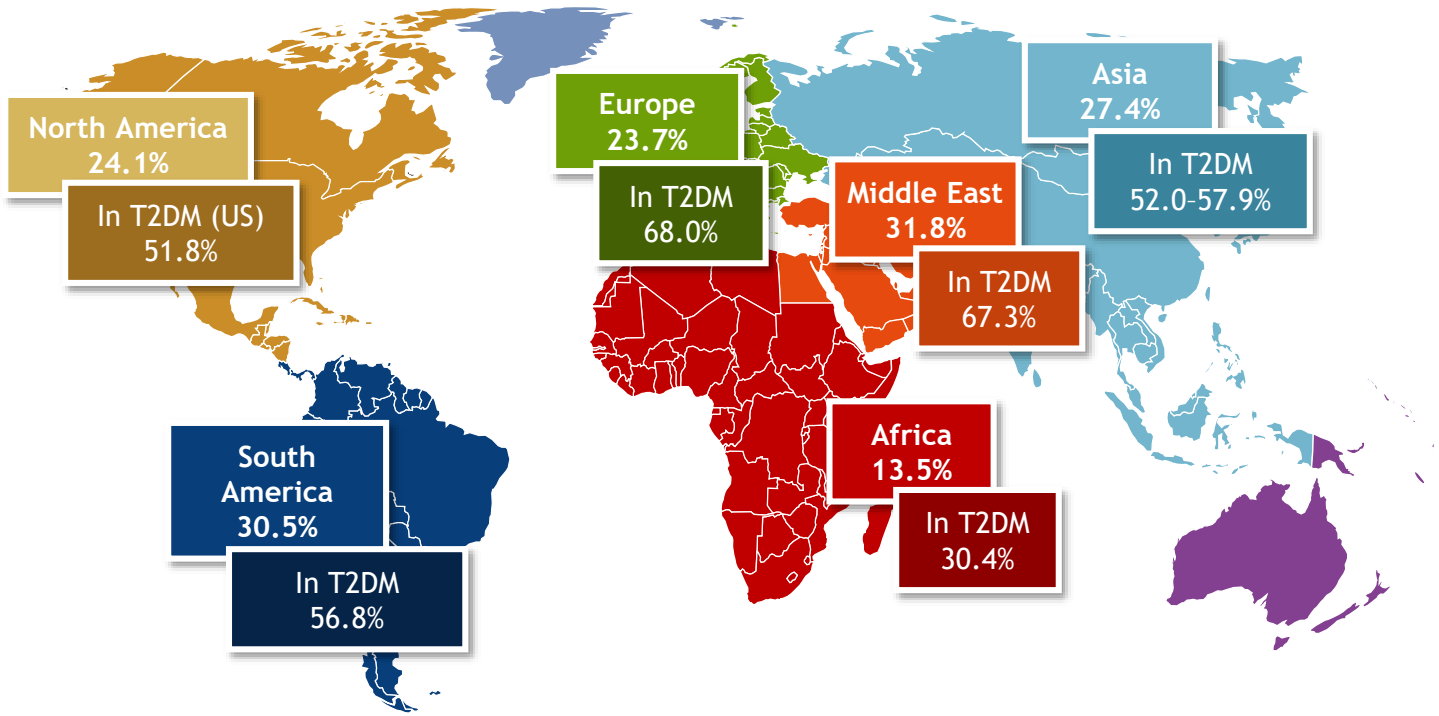
Obesity and diabetes, a growing burden of disease, is strongly associated with NASH



Worldwide prevalence of NAFLD is **25%**[1]

Worldwide prevalence of NAFLD among people with T2DM is **55-60%**[2]

Worldwide prevalence of NAFLD among people with obesity is between **70–80%** and even over **90%** among morbid obesity[3]

- Prevalence of NASH in general population is between 1.5–6.45%[1]
- Prevalence of NASH among T2DM is 37.3% (24.7–50.0%)[2]

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM: type 2 diabetes mellitus.

1. Younossi et al. Hepatology. 2016;64(1):73-84; 2. Younossi et al. J Hepatol. 2019;71:793-801; 3.Polyzos et al. Metabolism. 2019;92:82-97.

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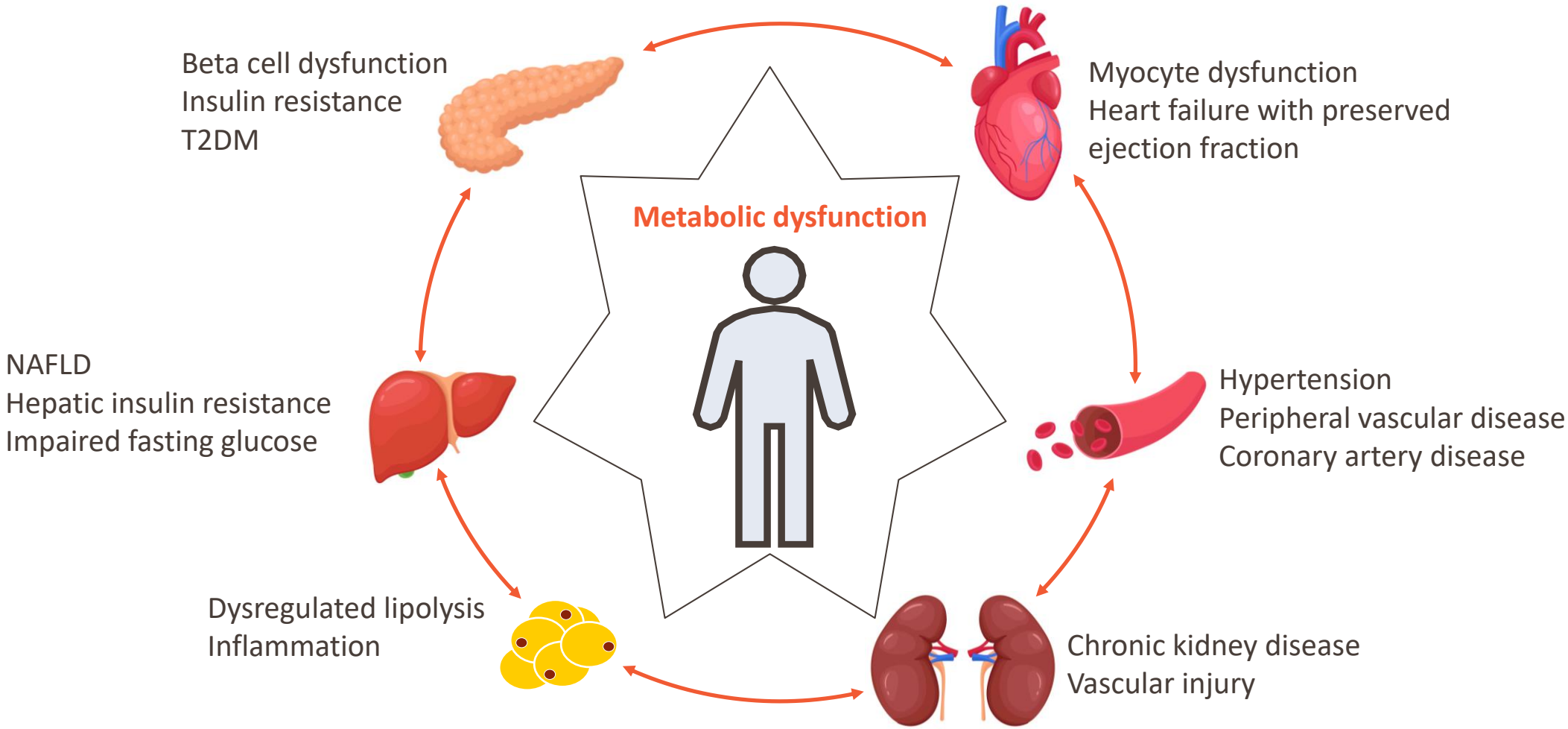
NAFLD is associated with metabolic dysregulation



NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.
Adapted from: Chakravarthy and Neuschwander-Tetri. Endocrinol Diabetes Metab 2020;3(4):e00112.

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Risk factors and conditions associated with NAFLD

Common conditions with established association	Other conditions associated with NAFLD
Obesity	Hypothyroidism
T2DM	Obstructive sleep apnea
Dyslipidemia	Hypopituitarism
Polycystic ovary syndrome	Hypogonadism
*Metabolic syndrome	Psoriasis

- *Metabolic syndrome is defined by the presence of ≥3 of the following features or established conditions:
  - Obesity or waist circumference >102 cm in men or >88 cm in women
  - Triglyceride level ≥150 mg/dL or more
  - HDL cholesterol <40 mg/dL in men and <50 mg/dL in women
  - Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or on treatment for hypertension
  - Fasting plasma glucose level 110 mg/dL or greater

HDL, high-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

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

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Thyroid function and NAFLD

- Low thyroid function is a risk factor for NAFLD

	Strict normal (n=8267)	Low (n=1857)	P value
Age, y	41	48	<0.001
Female, %	50	62	<0.001
BMI, kg/m^2	26.4	27.7	<0.001
Waist, cm	91	94	<0.001
Arterial HTN, %	18	28	<0.001
Diabetes, %	5.3	7.3	<0.001
Total CT, g/l	2.0	2.1	<0.001
HbA1c, %	5.3	5.4	<0.001
NAFLD, %	**32**	**42**	**0.008**
NAFLD with fibrosis, %	**3.7**	**5.8**	**0.008**

Risk of NAFLD*

Low normal thyroid function	25%
Subclinical thyroid function	42%

**** vs strictly normal thyroid function***

- Low thyroid function in NAFLD is an independent predictor of all-cause and cardiovascular mortality
  - Increased overall and CV related mortality

Kim et al. Am J Gastroenterol. 2020 Sep;115(9):1496-1504.

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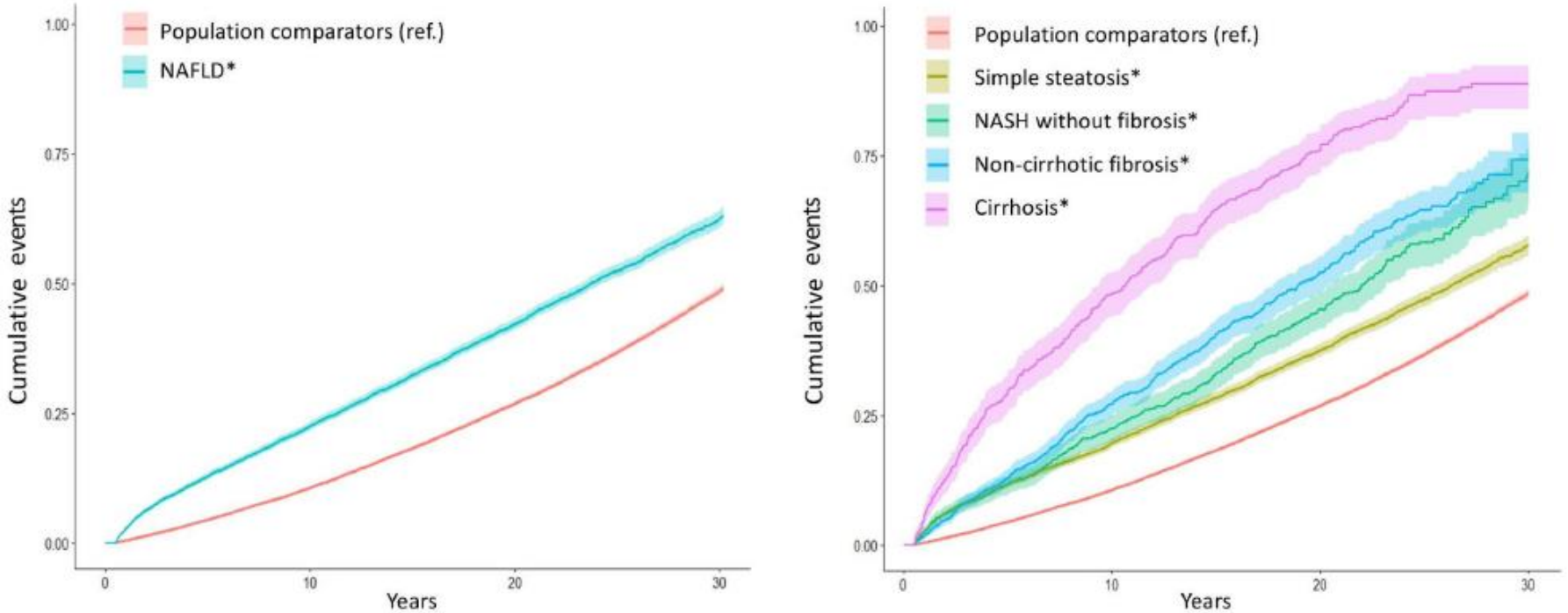
Patients with NAFLD have an increased risk of overall mortality

- All NAFLD histological stages were associated with significantly increased overall mortality, and this risk increased progressively with worsening histology



Cumulative incidence of all-cause mortality according to the presence and histological severity of NAFLD

HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

1. Simon et al Gut 2021;70:1375-1382..

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Patients with NAFLD have an increased risk for CV- and liver-related events

Outcome	Number
Death or OLT	**(n = 193)**
Cardiovascular disease	74 (38.3%)
Non-liver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
HCC	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8)
Other	35 (18.1%)
Pulmonary	5
Autoimmune disease	4
Renal failure	4
Accidents/trauma	10
Pancreatitis	2
Non-variceal GI bleeding	4
Surgery complications	2
Others	4
Unknown	15 (7.8)

Table from 1

CV, cardiovascular; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; OLT, orthotopic liver transplantation; T2DM, type 2 diabetes mellitus.

1. Angulo et al Gastroenterology. 2015;149(2):389-97.e10.;

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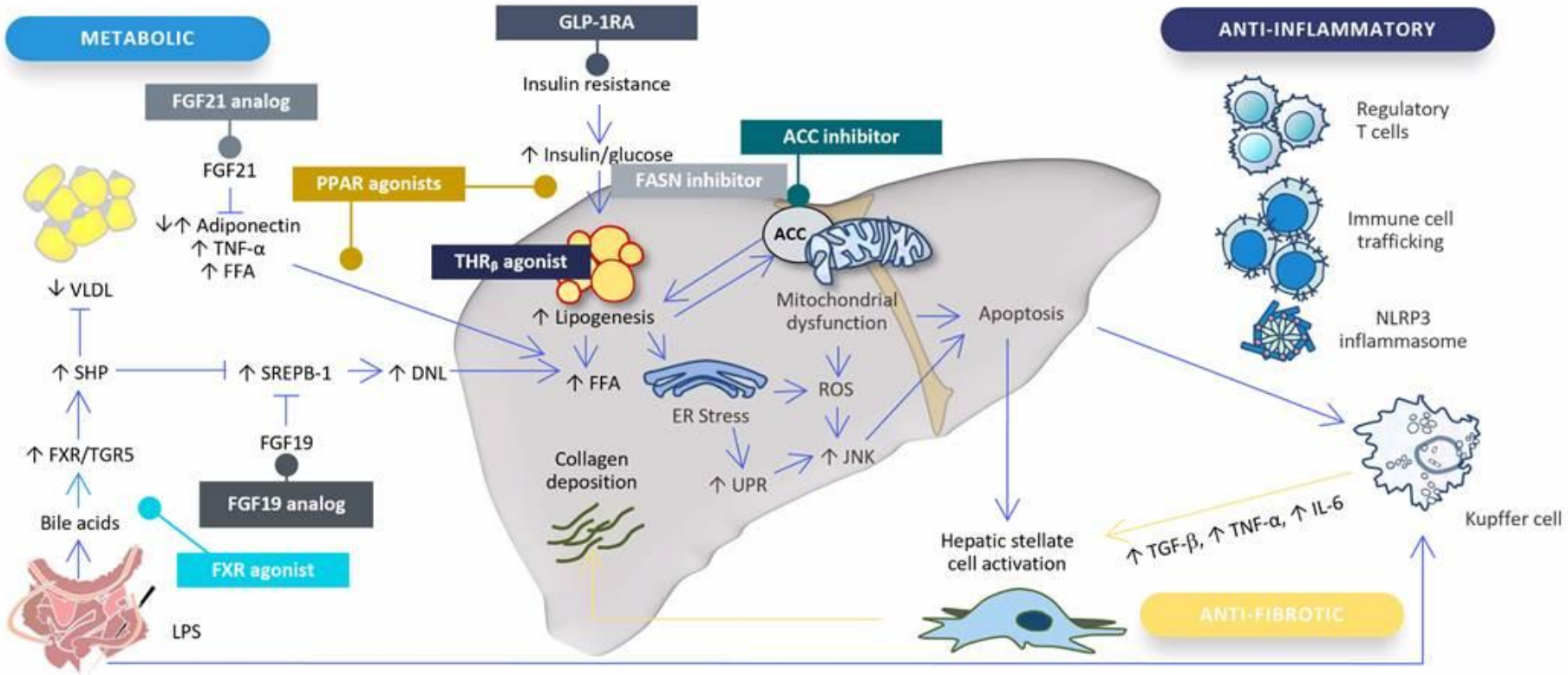
Pathways that contribute to NASH



Metabolic

Anti-Inflammatory

Anti-Fibrotic

Adapted from Konerman et al. J Hepatol. 2017; 68:362–375

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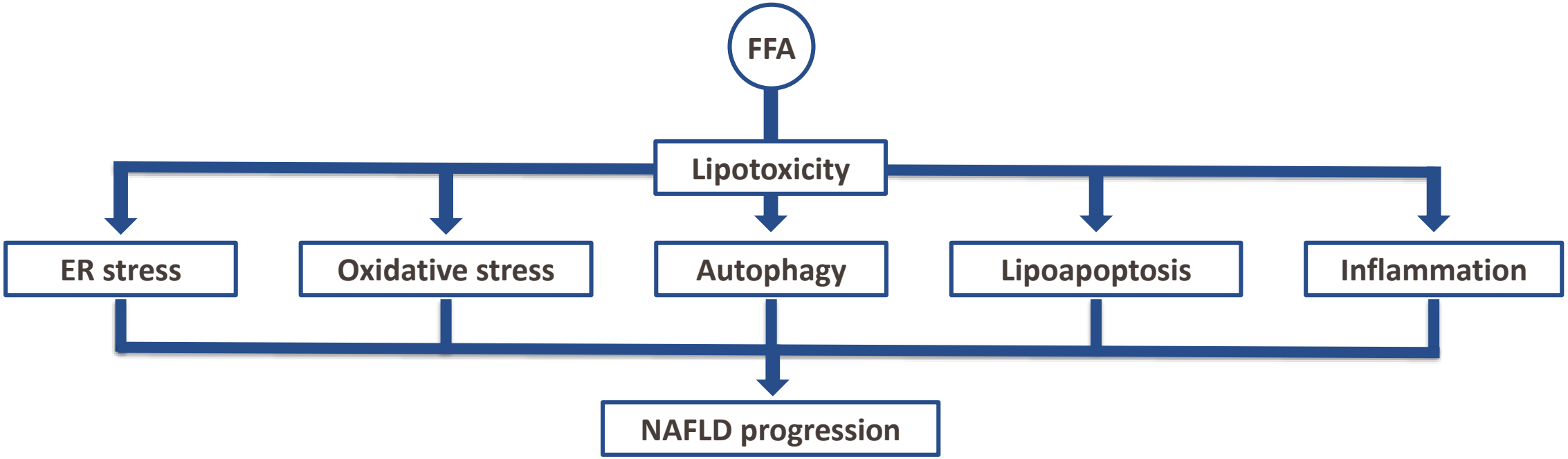
Lipotoxicity induces chronic liver injury, inflammation and fibrosis which contributes to NASH

- Lipotoxic effects mediated by FFAs contribute to NAFLD progression
  - FFAs-induced lipotoxicity promotes ER and oxidative stress, insulin resistance and impairs autophagy
  - As a consequence, FFAs activate apoptotic cascades thus promoting tissue damage and inflammation
- Altogether, these molecular events contribute to progression of NAFLD



ER, endoplasmic reticulum; FFA, free fatty acid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

1. Adapted from Rada et al. Cell Death and Disease. 2020;11:802.

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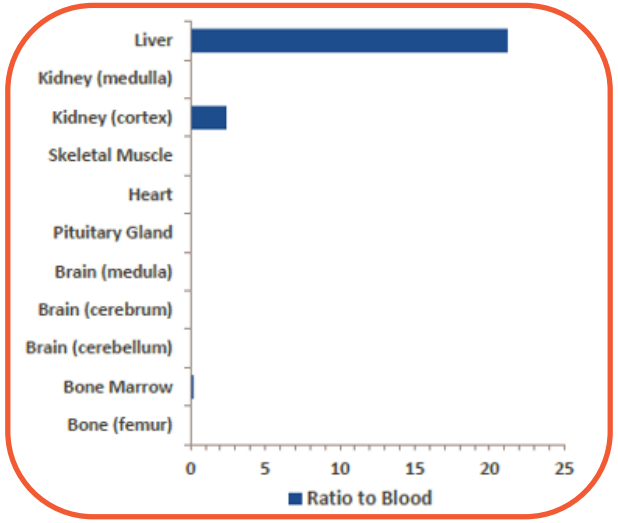
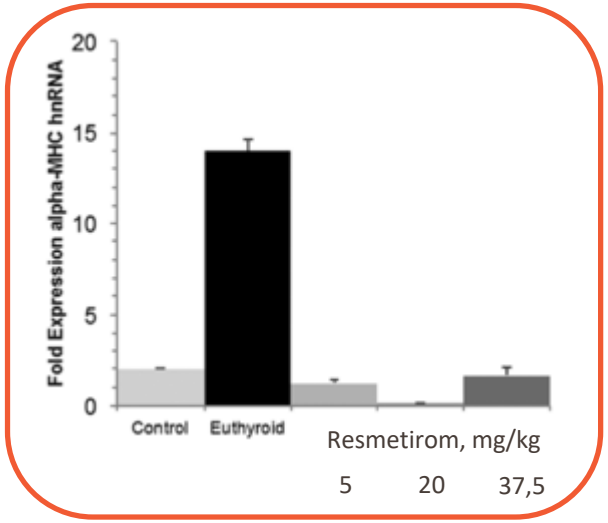
Resmetirom is a liver-directed, selective THR-β agonist

- Resmetirom is
  - 28 times more selective to THR-β than THR-α compared to T3[1]
  - Highly protein-bound and directed into the liver[2]
  - No THR-α activity, even at high concentrations[1]

Liver-directed[2]



Lack of effect in the heart[1]



THR, thyroid hormone receptor; T3, triiodothyronine

1. Kelly et al. J Med Chem. 2014; 57(10):3912-3923; 2. Madrigal data on file.

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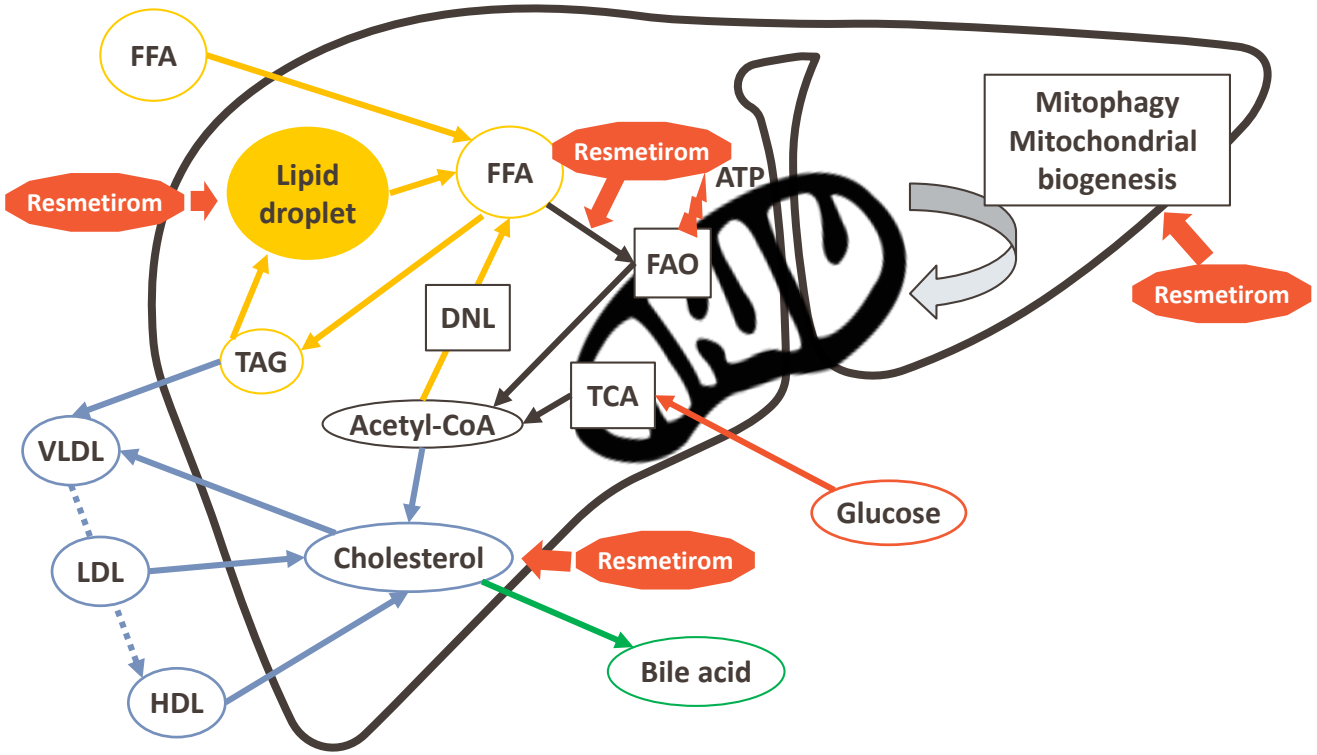
The Thyroid Hormone Receptor-β pathway plays a key role in hepatic lipid metabolism

- Thyroid hormones act on multiple pathways to maintain homeostasis in the liver by controlling:
  - *De novo* lipogenesis
  - Fatty acid oxidation
  - Mitophagy and mitochondrial biogenesis
  - Cholesterol metabolism
  - Carbohydrates metabolism
- THR-β is responsible for TH effects on metabolism and has a crucial and specific role in the liver
- THR-β agonism has been proven to have beneficial effects on lipid metabolism



DNL, *de novo* lipogenesis; FAO, fatty acid beta oxidation; FFA, free fatty acid; TAG, triacylglycerol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAG, triacylglycerol; TCA, tricarboxylic acid; VLDL, very low density lipoprotein. ATP, adenosine triphosphate; TH, thyroid hormones; THR, thyroid hormone receptor;

Ritter et al. Hepatology. 2020; 72(2):742-752; Saponaro et al. Front. Med. 2020; 7:331; Sinha et al. Nat Rev Endocrinol 2018;14(5):259-26; Taub R, et al. Atherosclerosis. 2013;230(2013):373-380; Taub et al. NASHTAG 2018 poster; Harrison SA, et al. Lancet. 2019;394(10213):2012-2024

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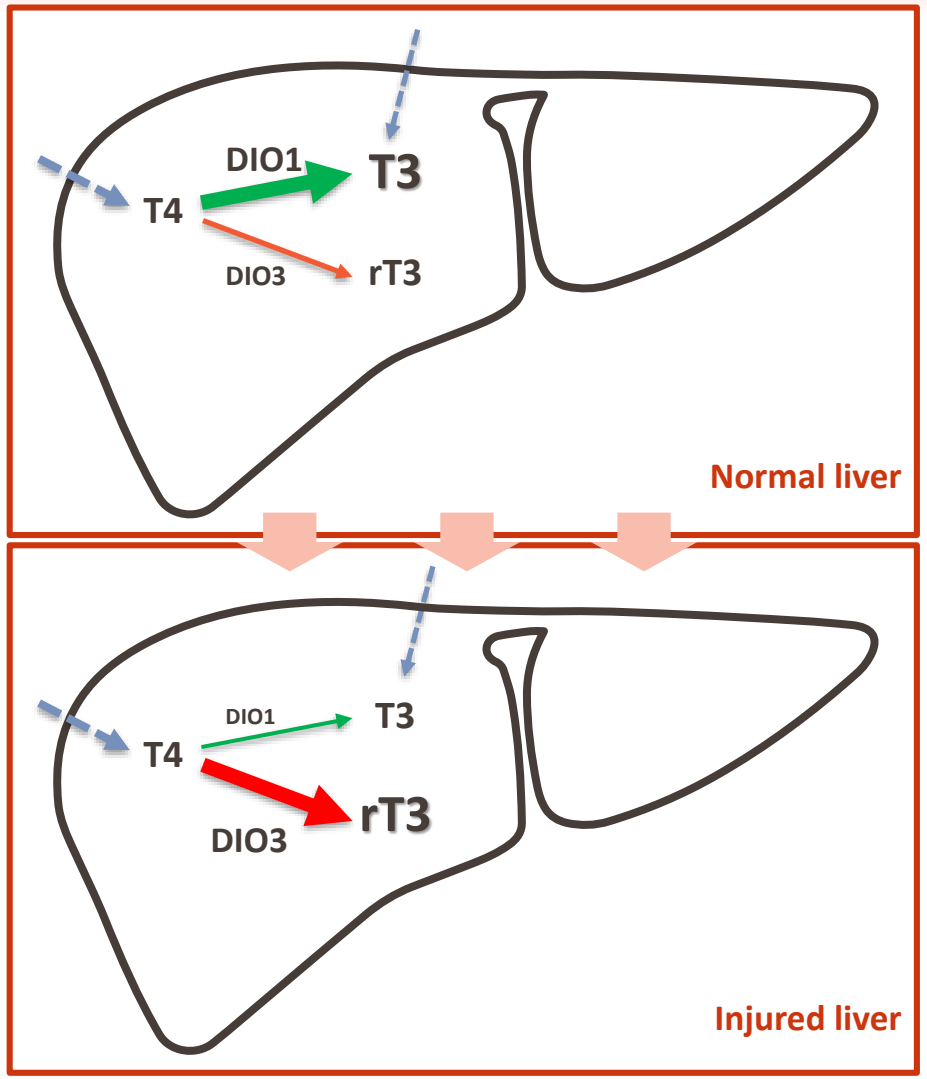
Chronic liver injury induces local hepatic dysfunction of the thyroid hormone pathway

- Local “intrahepatic hypothyroidism” observed during chronic liver injury, is caused by
  - Depressed conversion of prohormone T4 to active hormone T3 by DIO1 in favor of conversion to the inactive form rT3 by DIO3
  - This decrease of the T3/rT3 ratio results in a downregulation of the hepatic TH pathway



DIO1, deiodinase 1; DIO3, deiodinase 3; rT3, reverse T3; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone.
Bohinc et al Endocrinology. 2014;155(11):4591-601.

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Patients with NASH have dysregulated intrahepatic thyroid hormone pathway

- Comparing baseline demographics in two phase 2 studies with resmetirom
  - MGL-3196-05, phase 2 in patients with NASH
  - MGL-3196-06, phase 2 in patients with HeFH (non-NASH)
- There were no differences in baseline FT4 or TSH in NASH and HeFH patients of similar age
- RT3 was higher and FT3/RT3 lower in the NASH compared to the HeFH population suggesting a hypothyroid state in the NASH liver with reduced levels of active thyroid hormone, T3

Baseline	NASH	Non-NASH	Difference
n	125	116	
Mean age, years (SD)	50.3 (11.0)	57.3 (12.1)	
Male, n (%)	62 (49.6)	61 (52.6)	
White	117 (93.6)	115 (99.1)	
Hispanic	59 (47.2)	0	
BMI (SD) (kg/m2)	35.1 (6.1)	28.2 (4.2)	<0.0001
TSH (IU/L (SD)	2.01 (1.04)	2.02 (1.01)	0.93
FT4 (ng/dL) (SD)	1.13 (0.16)	1.13 (0.16)	0.86
FT3 (ng/dL) (SD)	3.18 (0.38)	3.06 (0.38)	0.015
Reverse T3 (ng/dL) (SD)	19.1 (5.)	14.8 (4.2)	<0.0001
Free T3/Reverse T3 (SD)	0.181 (0.065)	0.220 (0.57)	<0.0001

BMI, body mass index; DIO1, deiodinase 1; DIO3, deiodinase 3; HeFH, heterozygous familial hypercholesterolemia; FT4, free T4; FT3, free T3; NASH, non-alcoholic steatohepatitis; RT3, reverse T3; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.
Taub et al NASH-TAG 2020.

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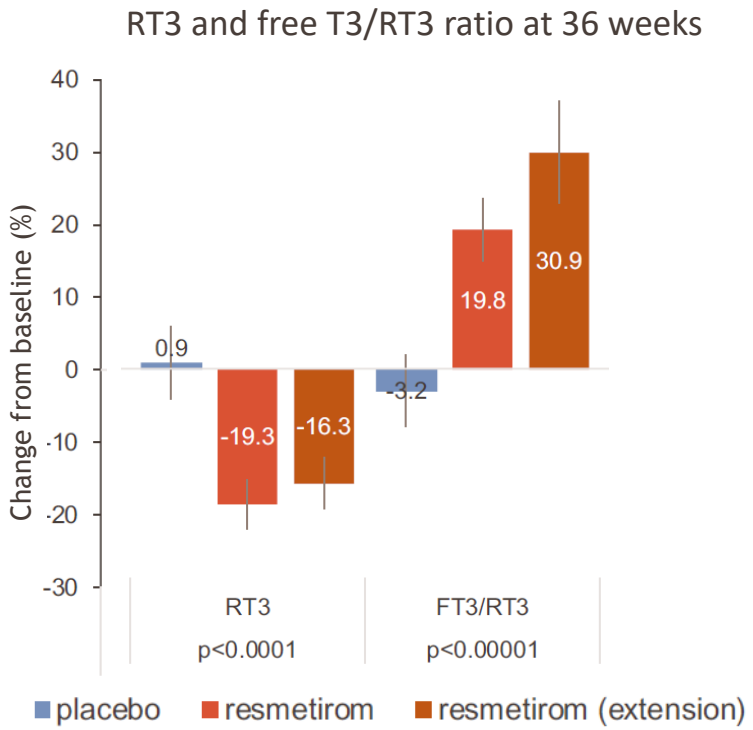
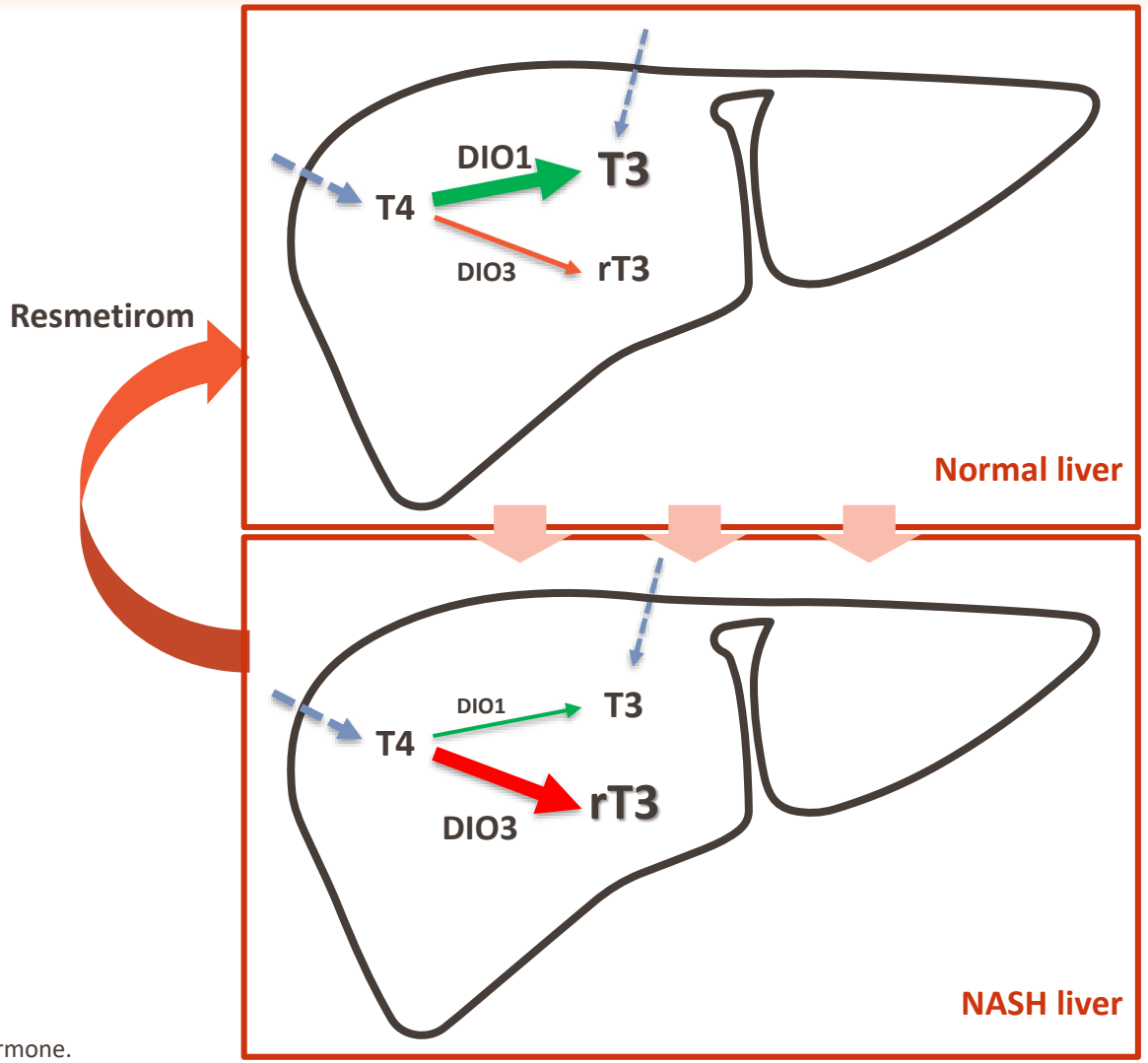
Resmetirom corrects endogenous thyroid hormone activity via increased direct THR-β activity

- Patients with NASH treated with resmetirom showed normalized RT3 levels[2,3]





DIO1, deiodinase 1; DIO3, deiodinase 3; rT3, reverse T3; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone.

1. Taub et al AASLD 2017 poster #1969 2. Taub et al NASH-TAG 2020 poster 3. Harrison et al. Hepatol Commun. 2021;0:1-16.

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Conclusions

- NAFLD is a highly prevalent disease, especially among patients with T2DM and obesity
- NAFLD increases the risk of CV-, liver-related and all cause mortality
- Thyroid hormones through the THR-β pathway, play instrumental roles in lipid metabolism in the liver. Thus, targeting the hepatic THR pathway is a promising strategy to treat NASH
- Resmetirom is a liver-directed, THR-β-selective agonist with no THR-α activity
- Resmetirom decreases lipotoxicity and reverses hepatic hypothyroidism in NASH patients potentially restoring normal liver function

CV, cardiovascular; FFA, free fatty acid; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; TH, thyroid hormones; THR, thyroid hormone receptor.

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Thanks!

Vlad Ratziu

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	The utilization of non-invasive technologies for the identification of NASH patients and monitoring of treatment response in the clinical setting	Jörn Schattenberg
	Resmetirom as a treatment for NASH: Updates from the MAESTRO Phase 3 clinical trials	Stephen Harrison
	Conclusion and final discussion	All

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The utilization of non-invasive technologies for the identification of NASH patients and monitoring of treatment response in the clinical setting

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Jörn M. Schattenberg, M.D.

Professor of Medicine and Director of the Metabolic Liver Research Program at the University Medical Center Mainz, Germany

Scientific work focuses on the identification and validation of biomarker and therapeutic approaches in chronic liver disease.

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joern.schattenberg@unimedizin-mainz.de

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Disclosures

Symposium is sponsored by Madrigal

- **Consultancy:** BMS, Boehringer Ingelheim, Genfit, Gilead Sciences, Intercept Pharmaceuticals, Madrigal Pharmaceuticals, Novo Nordisk, Nordic Bioscience, Novartis, Pfizer, Roche, Sanofi, Siemens Healthcare GmbH
- **Research Funding:** Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH
- **Speakers honorarium:** Intercept Pharmaceuticals, Falk Foundation MSD Sharp & Dohme GmbH

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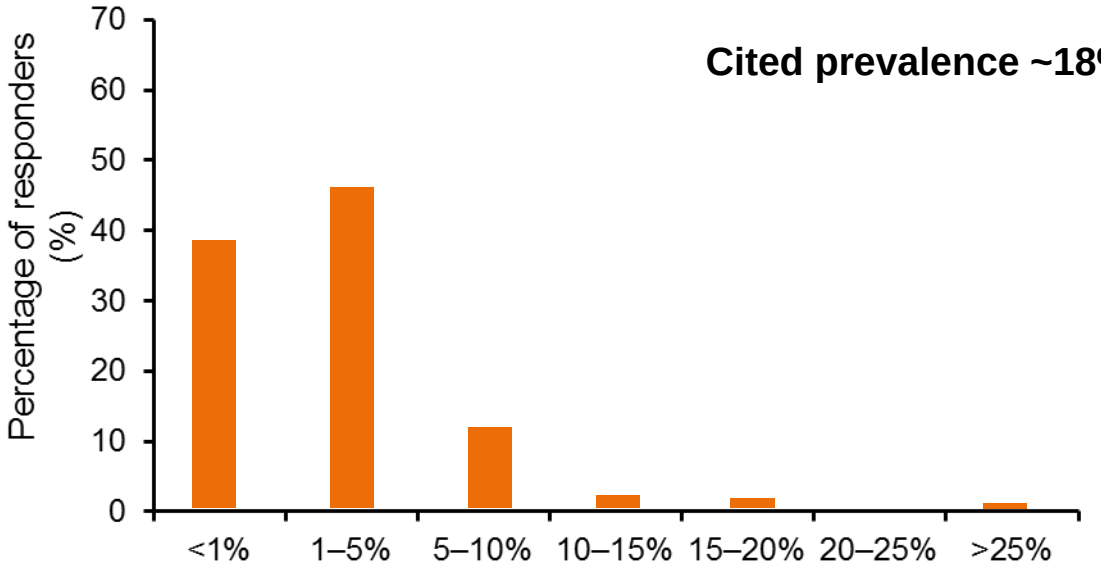
The challenge of identifying NASH with significant fibrosis[1]

Patients are not identified

What proportion of all the patients that you see in clinic with diabetes do you think have advanced liver fibrosis or cirrhosis?[2]



The prevalence of advanced fibrosis was underestimated by respondents

NASH, non-alcoholic steatohepatitis.

1. Marjot T, et al. Diabet Med 2018;35:89–98; 2. Online survey of 133 diabetes specialists in the UK.

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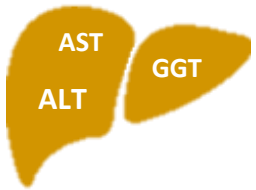
Guidelines ALREADY provide recommendations for screening and diagnosing patients with NASH and fibrosis

WHO should be screened for NAFLD?

≥50 years old

Metabolic syndrome/obesity

Type 2 diabetes



Abnormal liver enzymes

Steatosis

Insulin resistance

WHAT, WHY and HOW: assessments

Serum biomarkers

Fibrosis scores

Transient elastography

Acceptable **non-invasive tests** for identifying cases at **low risk.** Use in combination may confer additional diagnostic accuracy

Selection of patients at risk for management

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
EASL–EASD–EASO Clinical Practice Guidelines; J Hepatol. 2016;64:1388–1402.

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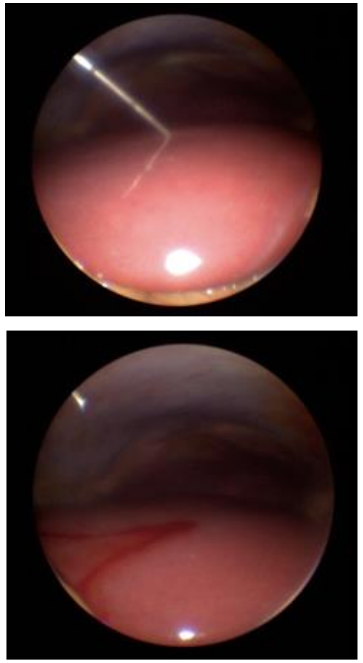
Why do we need non-invasive tests?

- NAFLD is a heterogeneous disease
  - Difficult to fully assess in one liver biopsy
- Liver biopsy is invasive
- Variability in the histological assessment
- Dynamic disease nature not captured in one “snap-shot“ assessment
- High unmeet need for non-invasive biomarkers and imaging to accurately diagnosis NASH and monitor progression/regression – link to outcome!



Laparoscopic liver biopsy
J. Schattenberg

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

1. Brunt et al.Hepatology. 2021;73(5):2028-2038. 2. Angulo et al. Gastroenterology. 2015;149(2):389-97.e10.

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What does the perfect non-invasive test look like?

- Exact and reproducible
- Available and cheap
- Validated across different populations
  - Age, ethnic
- Diagnostic biomarker
  - Detect fibrosis stages
- Monitoring biomarker
  - Treatment response
- Prognostic biomarker
  - Predicts clinical events/outcome

Long et al. Metabolism 2020;111S:154259; Patel et al. JHEP Rep 2020;2:100067;Noureddin et al. Hepatol Commun 2020;**4:**141-144; https://perspectum.com/pharma-solutions/nash (accessed May 2021); https://www.echosens.com/ (accessed May 2021)

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How to diagnose NASH with fibrosis using non-invasive approaches?

BLOOD

Markers

Indirect: AST, ALT, platelets, bilirubin, prothrombin time, albumin

Direct: α2 macroglobulin, hyaluronate, TIMP1, PRO-C3

Tests

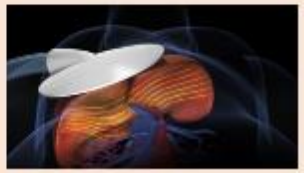
APRI, FIB4, eLIFT NAFLD fibrosis score

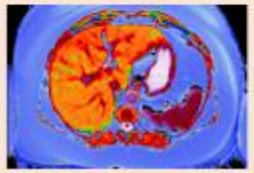
FibroMeter, Fibrotest, Hepascore, ELF

IMAGING

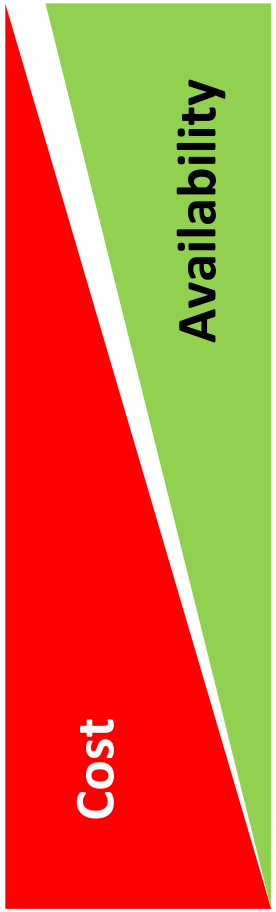
Transient Elast.

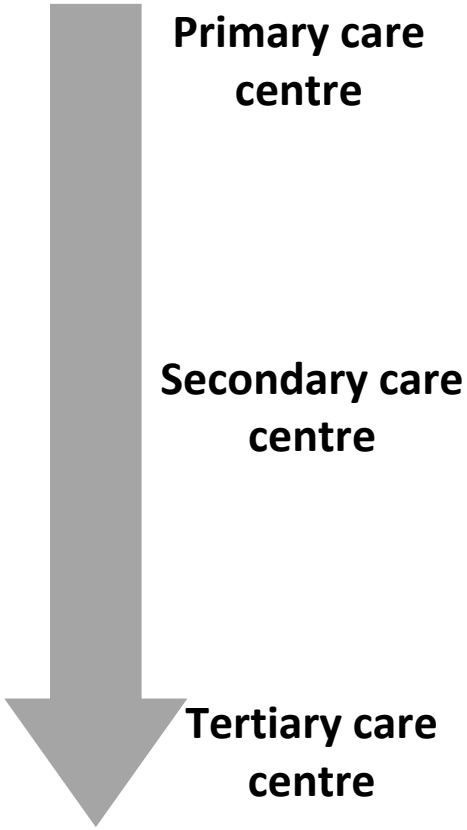
Point SWE / 2D SWE





MRI MRE





ALT, aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; PRO-C3, N-terminal type 3 collagen propeptide; SWE, shear wave elastography; TIMP, tissue inhibitor metalloproteinase; 2D SWE, two dimensional SWE.

Crossan C, et al. Health Technol Assess 2015;19:1–409 (Appendix 9).

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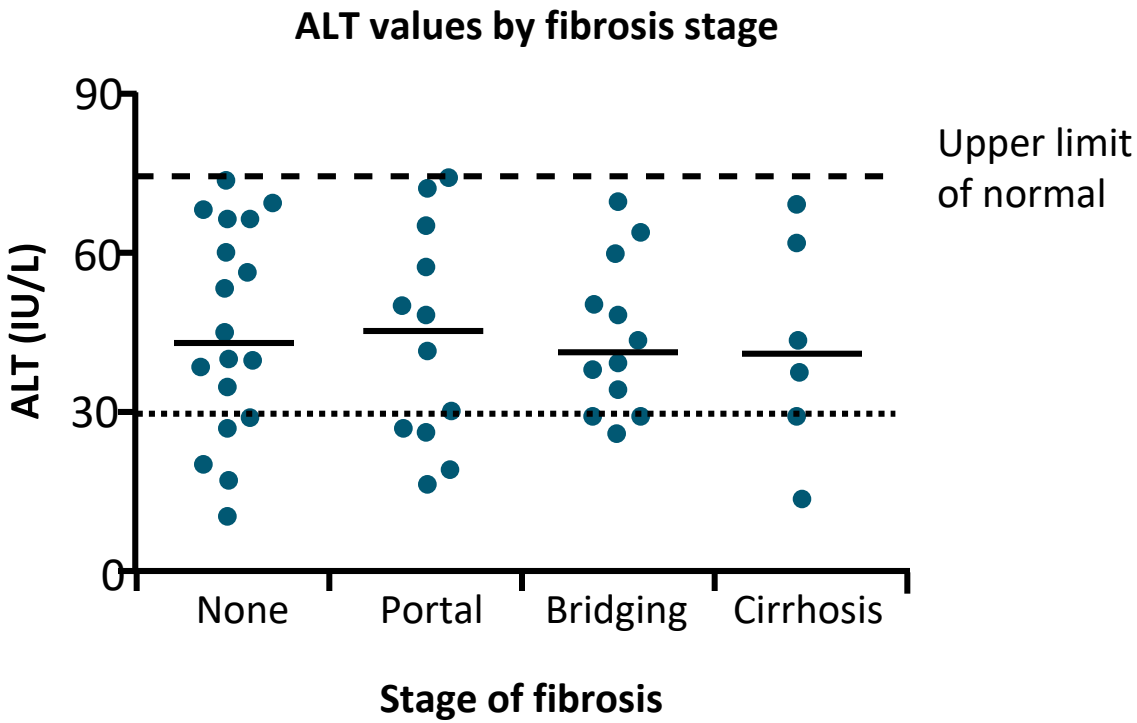
NAFLD grade and stage, Similar with normal vs abnormal liver enzymes

Pattern	Normal ALT (n = 51)	Abnormal ALT (n = 50)	p-value
Fat alone, n	8	10	NS
Fat + scattered inflammation, n	8	10	NS
Fat + ballooning ± inflammation, n	13	11	NS
Fat + ballooning ± Mallory hyaline ± pericellular fibrosis, n	22	19	NS



ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; NS, non significant.
Mofrad et al. Hepatology. 2003 Jun;37(6):1286-92.

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Combined scores, utilizing “best-of” in each category

Test	Requirements	Target condition	Components
MACK-3[1]	Blood test	Fibrotic NASH (NAS≥4 and F≥2)	AST, HOMA and CK-18
ADAPT/Pro-C3[2,3]	Blood test	Advanced fibrosis (≥F3)	Age, diabetes, PRO-C3, platelets
FAST[4]	Blood test and imaging	Fibrotic NASH (NAS≥4 and F≥2)	AST, VCTE, CAP

ADAPT, model including age, presence of diabetes, platelet count and PRO-C3; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CK-18, cytokeratin 18; F, fibrosis stage; FAST, FibroScan-AST; HOMA, homeostatic model assessment; MACK-3; combination of AST, HOMA and CK-18; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; PRO-C3; N-terminal type 3 collagen propeptide; VCTE, vibration-controlled transient elastography.

1. Boursier et al. Aliment Pharmacol Ther 2018;47:1387-1396; 2. Daniels et al. Hepatology. 2019 2019;69(3):1075-1086; 3. Schattenberg and Loomba, R. Hepatology. 2019;69:934-936; 4. Newsome, et al. Lancet Gastroenterol Hepatol 2020;5:362-373.

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The FAST score to identify patients with active NASH disease

- The FibroScan-AST score aims to identify patients with NASH, NAFLD activity score ≥4, and fibrosis stage ≥2[1]
- Components AST, VCTE and CAP[1]

	AUROC	n	Prevalence of NASH + NAS≥4 + F≥2	Rule-out zone (FAST≤0.35)				Grey zone (FAST 0.36-0.66)	Rule-in zone (FAST≥0.67)			
			n (%)	n (%)	Sensitivity	Specificity	NPV	n (%)	n (%)	Sensitivity	Specificity	NPV
Derivation cohort	0.80 (0.76-0.85)	350	174 (50%)	113 (32%)	0.90 (157/174)	0.53 (93/176)	0.85 (93/110)	136 (39%)	101 (29%)	0.90 (159/176)	0.48 (84/174)	0.83 (84/101)
Pooled external cohort	0.85 (0.83-0.87)	1026	277 (27%)	517 (51%)	0.89 (246/277)	0.64 (483/749)	0.94 (483/514)	312 (30%)	197 (19%)	0.92 (688/749)	0.49 (136/277)	0.69 (136/197)

AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; F, fibrosis stage; FAST, FibroScan-AST; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; VCTE, vibration controlled transient elastography.

1. Newsome et al. Lancet Gastroenterol Hepatol. 2020;5(4):362-373; 2. Eddowes et al. Gastroenterology. 2019;156(6):1717-1730.

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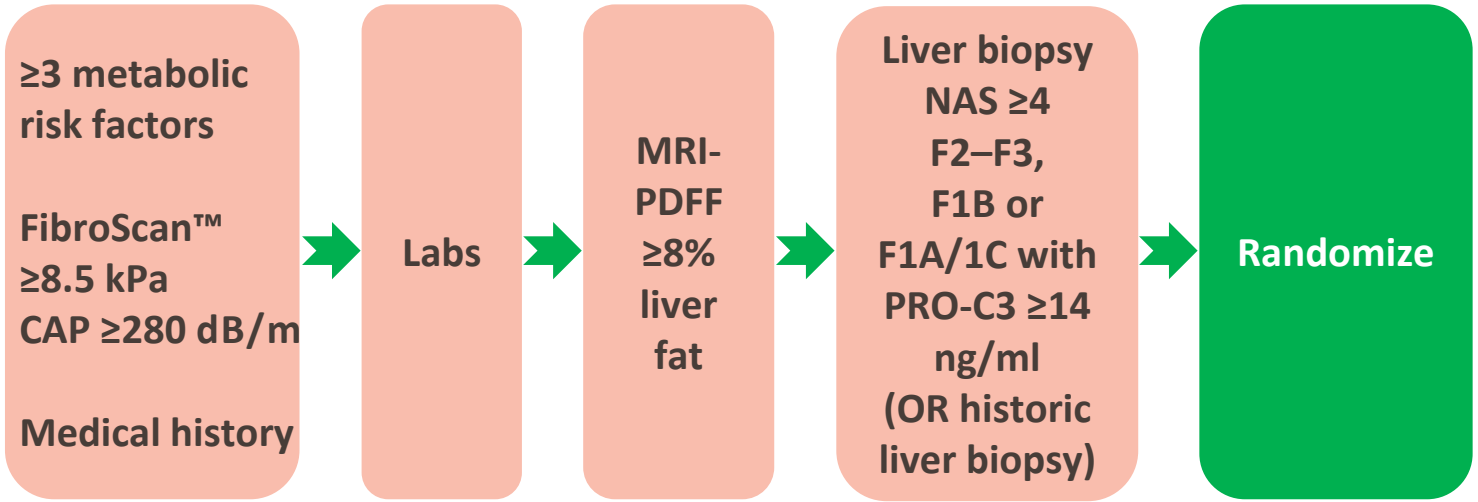
MAESTRO-NASH: A sequential patient identification algorithm

Risk factors for NASH
Age >50y
BMI >30 kg/m^2
Elevated liver enzymes
T2DM
Hypertension
Dyslipidemia
Metabolic syndrome
Historical FibroScan™ >8.5 kPa, CAP >280 dB/m

MAESTRO-NASH, 8 Week screening process[1]



Enrolling patients in NASH fibrosis studies is particularly challenging because most patients at the time of screening do not have a definite diagnosis of NASH and their fibrosis stage is unknown

BMI, body mass index; CAP, controlled attenuation parameter; kPa, kilopascal; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; PRO-C3, N-terminal type 3 collagen propeptide; T2DM, type 2 diabetes mellitus.

1. Harrison et al AASLD 2020 abstract #1657.

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MAESTRO-NASH screening algorithm improves study qualification at biopsy

Qualifying liver biopsies with NAS ≥4, all components, F1–F3	%	Total
Fibrosis stage F2–F3	60.3	
Fibrosis stage F1B or F1A/C with PRO-C3>14 ng/mL	10.3	
Total qualifying biopsies		**70.6%**
Non-qualifying biopsies with NASH, F1–F4		
NAS=3 with F2–F3 fibrosis	3.2	
F1 NAS=3, all components	1.8	
F4 NASH cirrhosis	2.2	
NAS≥4 F1A/C with PRO-C3<14 ng/mL	3.2	
Total non-qualifying biopsies with NASH		**10.5%**
Total biopsies with NASH		**81.1%**
Total biopsies without definite NASH or with F0 NASH		**18.8%**

- ~70% of biopsies met eligibility requirements after advancing through the algorithm
- ~80% had NASH, some with NASH cirrhosis, or advanced NASH (F2-F3) with NAS <4

F, fibrosis stage; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; PRO-C3, N-terminal type 3 collagen propeptide.
Harrison et al AASLD 2020 abstract #1657.

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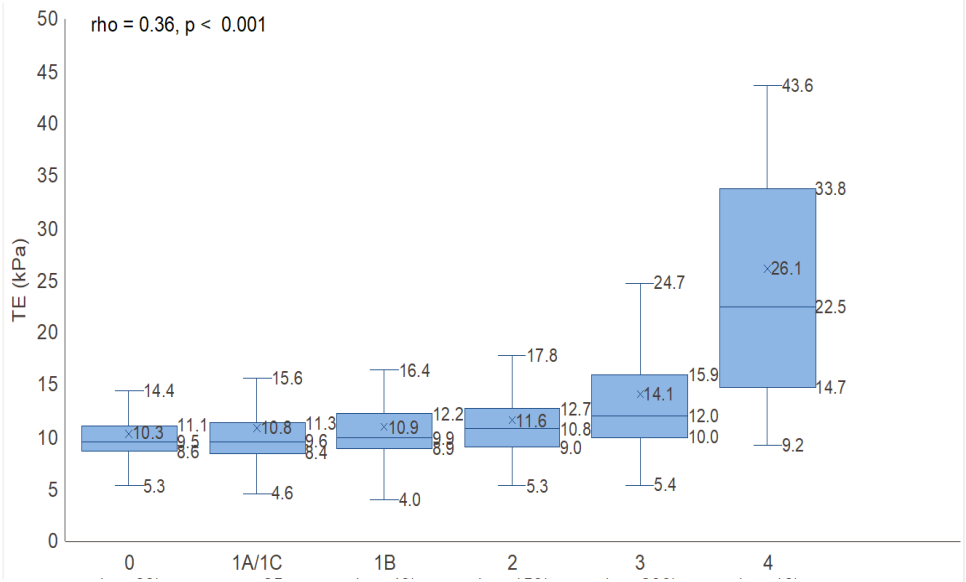
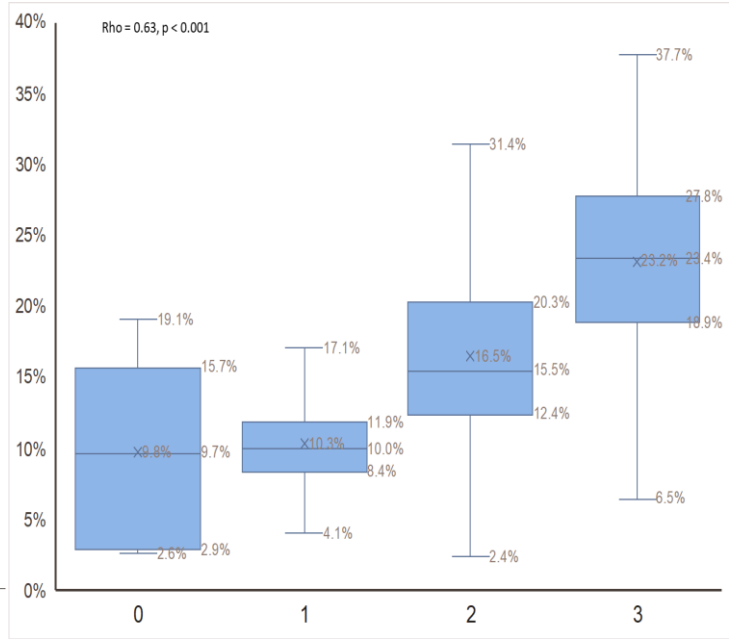
MAESTRO-NASH: FibroScan, MRI-PDFF and MRE at screening correlates with histology[1]

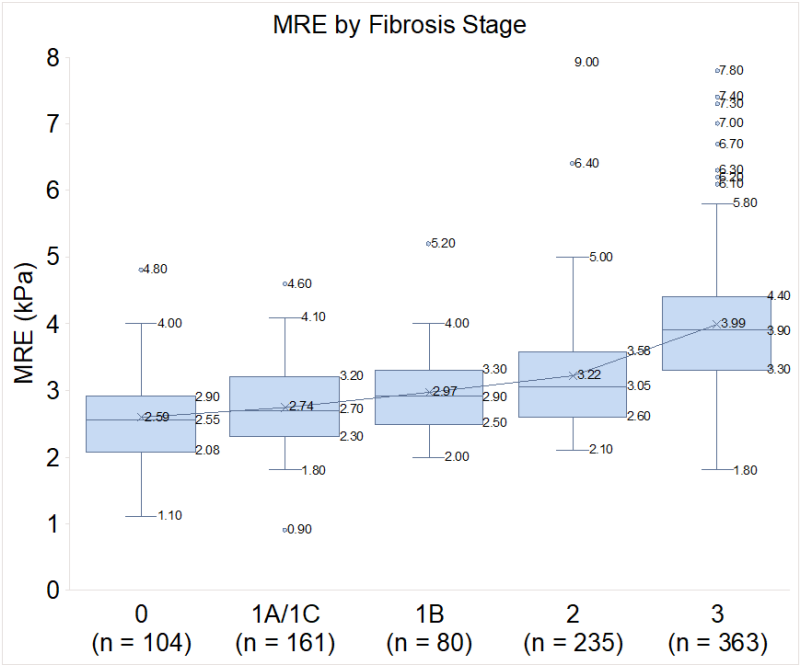
Correlation of FibroScan TE by fibrosis stage



Correlation of PDFF ≥8% with steatosis



Correlation of MRE kPa by fibrosis stage



Screening data from the MAESTRO-NASH Phase 3 trial[2]

kPa, kilopascal; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; TE, transient elastography.

1. Harrison et al. Poster at AASLD Emerging Topic 2021; 2. ClinicalTrials.gov NCT03900429.

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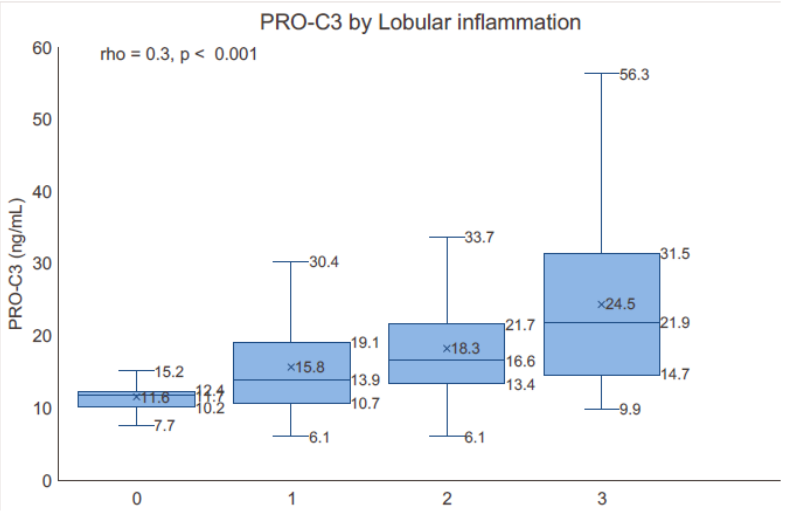
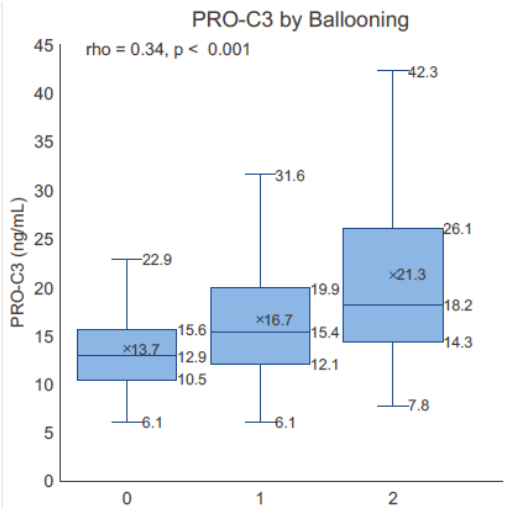
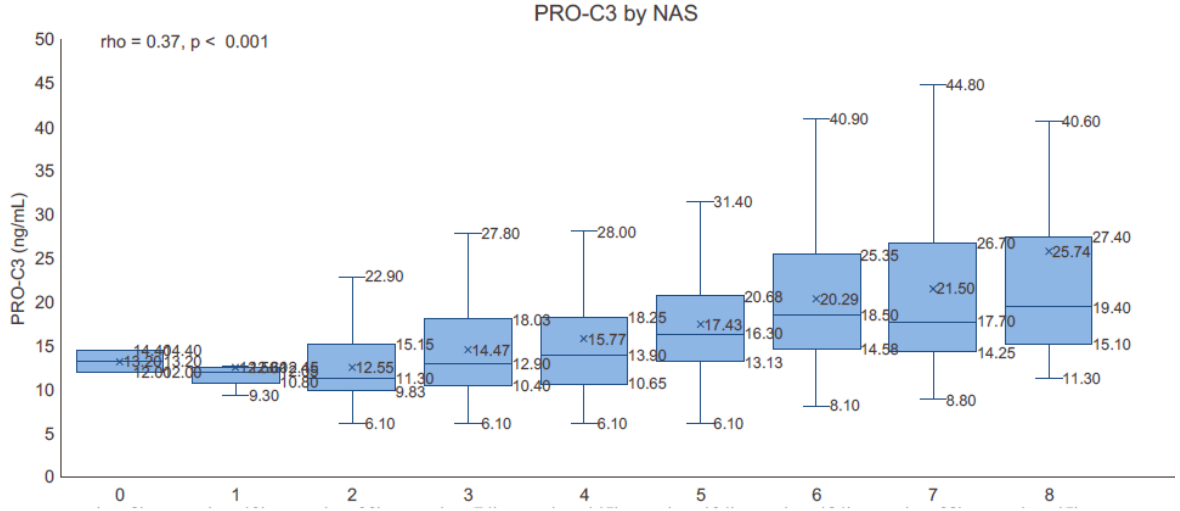
MAESTRO-NASH: PRO-C3 at screening correlates with inflammation, ballooning and NAS

In the first ~1000 patients screened in MAESTRO-NASH[1], the data was assessed for associations between PRO-C3 and component of the NAS score on liver biopsy using Spearman's correlation test.







In the absence of a liver biopsy, elevated PRO-C3 (or FIBC3[2]) in the setting of metabolic syndrome, increased liver stiffness and MRI-PDFF may predict for NASH[3]

BMI, body mass index; FIBC3, score comprised of PRO-C3, age, BMI, T2DM and platelets; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; PRO-C3, N-terminal type 3 collagen propeptide; T2DM, type 2 diabetes mellitus.

1. NCT03900429; 2.Boyle et al. JHEP Rep. 2019;1(3):188-198; 3. Harrison et al. AASLD 2020 poster #1657.

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Monitoring NASH treatment effects non-invasively

- In real life serial liver biopsies will be an uncommon way to monitor NASH patients with significant liver fibrosis

- Several serial non-invasive tests and imaging can be used to adequately monitor treatment responses in NASH patients with significant liver fibrosis
  - Steatosis: CAP and MRI-PDFF
  - Inflammation/ballooning: Liver enzymes; CK-18
  - Fibrosis: Serum biomarkers, PRO-C3, ELF; imaging, FibroScan, MRE

CAP, controlled attenuation parameter; CK-18, cytokeratin 18; ELF, enhanced liver fibrosis; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NASH, non-alcoholic steatohepatitis; PRO-C3, N-terminal type 3 collagen propeptide.

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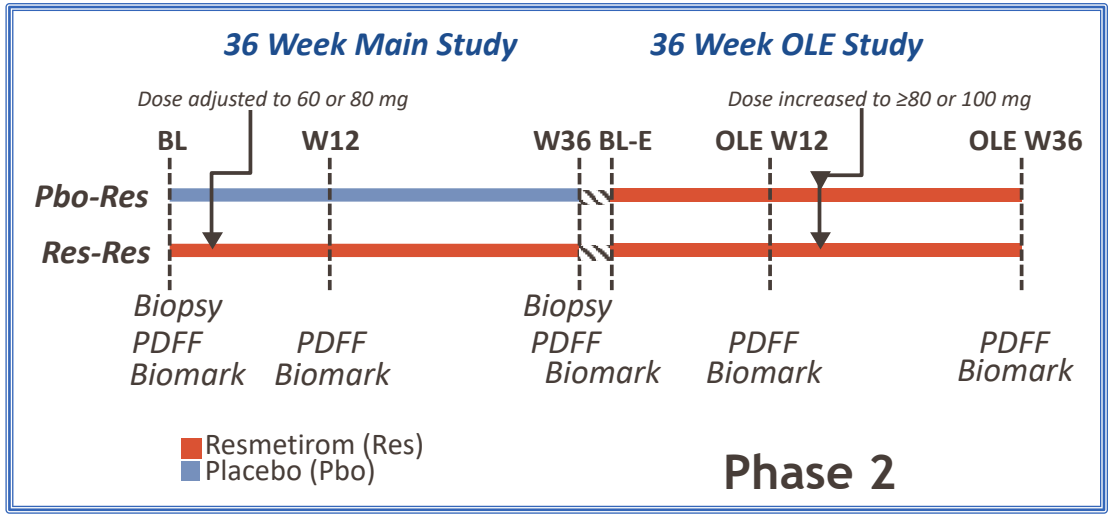
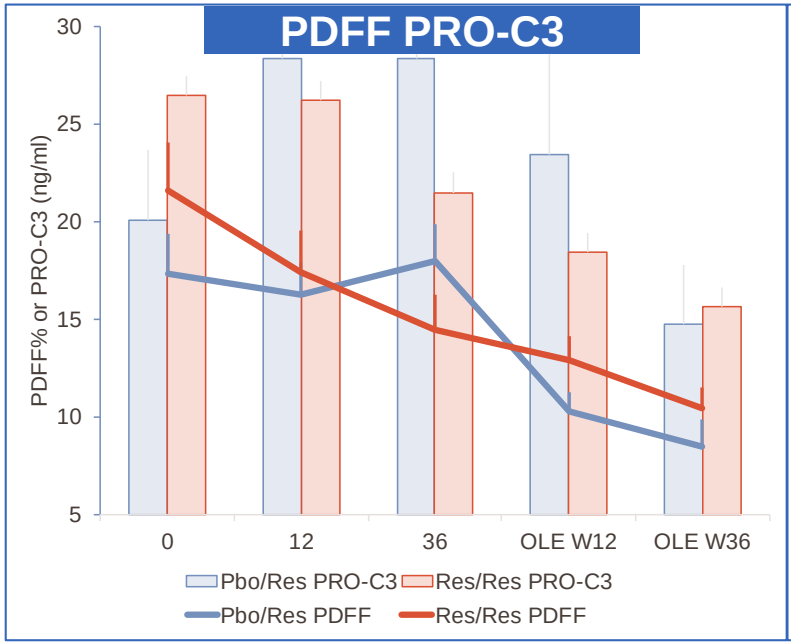
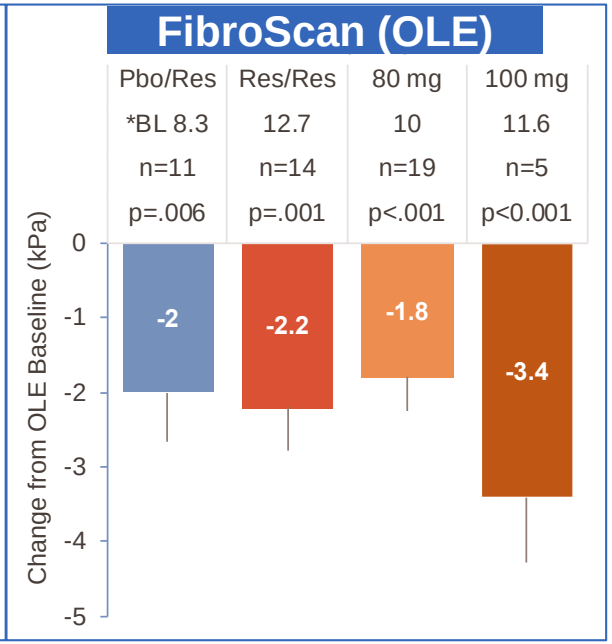
Response to resmetirom by PRO-C3, MRI-PDFF and FibroScan in Phase 2







BL, baseline; PDFF, proton density fat fraction; Pbo, placebo; PRO-C3, N-terminal type 3 collagen propeptide; OLE, open label extension study; Res, resmetirom.
Harrison et al. Hepatol Commun. 2021;0:1-16.

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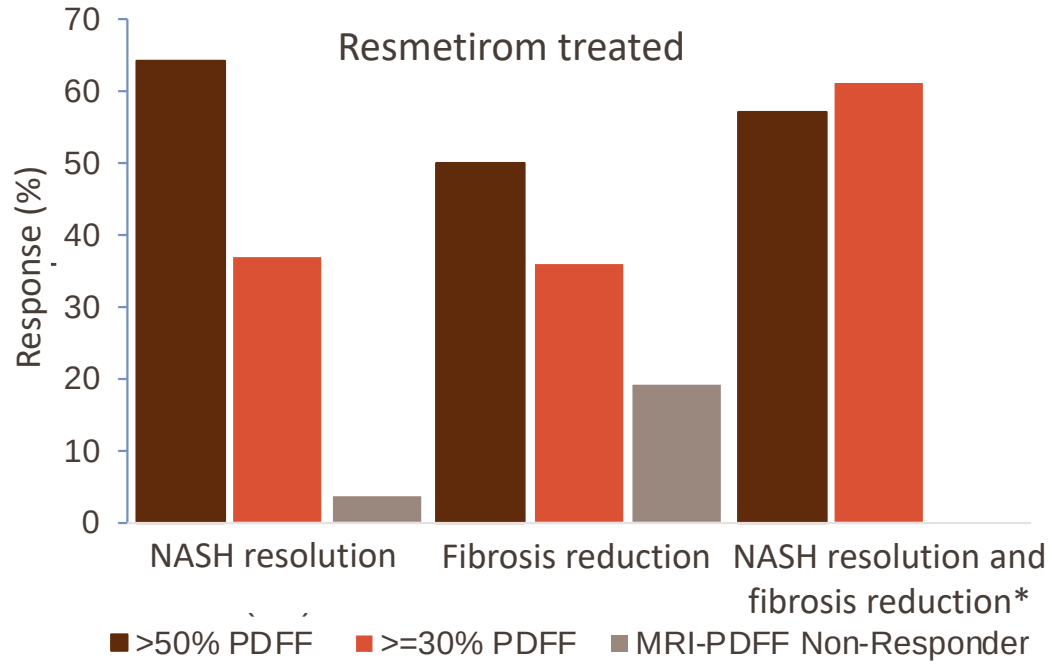
The decrease in liver fat measured by MRI-PDFF in Phase 2 is associated with histological improvement

- Percentages of patients with NASH resolution increased with greater PDFF reduction
- In patients treated with resmetirom and ≥ 50% fat reduction at Week 12, 64% had NASH resolution with a component response driven primarily by ballooning and inflammation
- PDFF reduction ≥ 30 and ≥ 50% at Week 12 was also associated with
  - Fibrosis reduction on subsequent liver biopsy
  - Achievement of both endpoints: NASH resolution and ≥ 1 point fibrosis reduction



Non Responder: <30% fat reduction on Week 12 MRI-PDFF

* % fibrosis reduction in biopsies with NASH resolution.

CAP, controlled attenuation parameter; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis.

Loomba et al. EASL 2020 Oral presentation; 3. Harrison et al. Hepatol Commun. 2021;0:1-16.

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MAESTRO-NAFLD-1: Resmetirom (100 mg) reduces liver fat (MRI-PDFF) and liver stiffness (MRE)

	All	SHBG (high)
MRI-PDFF (%)		
Baseline (%)	17.6	17.9
Relative % change	−53%	−62%
p-value	<0.0001	<0.0001
MRE (kPa)		
Baseline (≥2.9)	3.5	3.5
Absolute change	−0.34	−0.46
p-value	0.003	0.003

Week 16 MRI-PDFF (%) and MRE (kPa) change from baseline

- MRI-PDFF reduction of 53% fat fraction overall, and MRE (-0.34) were observed at Week 16[1]
- MRE, unlike other elastography techniques, provides a stiffness map (elastogram)
  - The volume of liver parenchyma assessed with a single slice of MRE is about 250 cm3[2]

kPa, kilopascal; MRI-PDFF, magnetic resonance imaging proton density fat fraction; MRE, magnetic resonance elastography; SHBG, sex hormone-binding globulin.

1. Harrison et al. AASLD 2020 abstract #1707. 2. Hoodeshenas et al. Top Magn Reson Imaging. 2018;27(5):319-333.

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Conclusions

- Biopsy will not be utilized for identification and monitoring of patients with non-cirrhotic NASH with liver fibrosis. Non-invasive technologies are the future
- Utilization of non-invasive technology based algorithms allow for dynamic assessment of fibrotic and inflammatory liver disease
- The MAESTRO clinical trial program will contribute data from over 2,000 patients to validate a real-world pathway for treating physicians to identify and monitor patients with NASH therapeutics
- Resmetirom produces significant reductions in liver fat, liver stiffness and biomarkers of liver fibrosis as determined by non-invasive technologies

NASH, non-alcoholic steatohepatitis.

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Thanks!

Jörn Schattenberg

Madrigal Satellite Symposium

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Phase 3 development of resmetirom, a liver-directed thyroid hormone receptor (THR)-β agonist for the treatment of patients with NASH and significant liver fibrosis

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Phase 3 development of resmetirom, a liver directed thyroid hormone receptor (THR)-β agonist for the treatment of patients with NASH and significant liver fibrosis

Madrigal Satellite Symposium agenda

Time	Topic	Speaker
	Welcome and introduction	Stephen Harrison
	The contribution of metabolic co-morbidities and hepatic thyroid hormone dysregulation to the pathophysiology of NASH	Vlad Ratziu
	The utilization of biomarkers for the identification of NASH patients and as predictors of treatment response in the clinical setting	Jörn Schattenberg
	Resmetirom as a treatment for NASH: Updates from the MAESTRO Phase 3 clinical trials	Stephen Harrison
	Conclusion and final discussion	All

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Resmetirom as a treatment for NASH: Updates from the MAESTRO Phase 3 clinical trials

Stephen Harrison

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Disclosures

- SAH consults, advises, received grants, and owns stock in Galectin, Genfit, Madrigal, Metacrine, NGM, and NorthSea. He consults, advises, and received grants from Axcella, Cirius, Hepion, CymaBay, Galmed, Gilead, HighTide, Intercept, Novartis, Novo Nordisk, and Sagimet. He consults, advises, and owns stock in Akero and HistoIndex. He consults and advises Altimmune, Blade, CiVi, Echosens, Forsite Labs, Gelesis, Indalo, Innovate, Medpace, Perspectum, Poxel, Prometic, Terns, and Viking. He received grants from Bristol-Myers Squibb (BMS), Conatus, Enyo, Immuron, Pfizer, Second Genome, and Tobira/Allergan.

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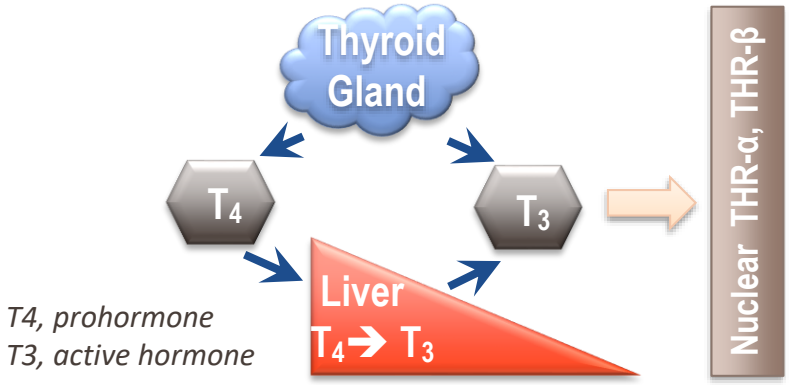
Resmetirom: Target and Phase 2 Results in the Treatment of NASH



Thyroid Hormone Pathway

Pleiotropic effects in the liver with potential for addressing the underlying metabolic syndrome and hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly and indirectly)

- *Reduction of liver fat through breakdown of fatty acids, normalization of mitochondrial and liver function*

- Resmetirom, is a once a day, oral liver-directed thyroid hormone receptor-β agonist that acts in the liver to improve histopathologic features of NASH
- In Phase 2, the primary endpoint was achieved: Liver fat reduction assessed by MRI-PDFF at Weeks 12, 36
- Reduction in PDFF of >=30% was associated with resolution of NASH and fibrosis improvement on biopsy
- Additional endpoints achieved: reduction in liver enzymes and fibrosis biomarkers; improvements in CV profile: LDL-cholesterol and lipid lowering; reduction in liver stiffness (fibrosis stage) on serial FibroScan, an office-based test

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Phase 3 NASH Clinical Trials, *Ongoing*: MAESTRO-NASH and MAESTRO-NAFLD-1

Compound/ Indication	Clinical Trial	Pre-Clinical	Phase 1	Phase 2	Phase 3	Description
Resmetirom (MGL-3196) Thyroid Hormone Receptor-β (THR-β) Agonist **Treatment of Nonalcoholic Steatohepatitis (NASH)**	**Phase 2 MGL-3196-05** NCT02912260	Completed				■ MRI-PDFF, liver biopsy: endpoints achieved[1] • 36 week with 36 week open-label extension
	Phase 3 MAESTRO-NASH NCT03900429	Recruiting →				■ Treatment of NASH with Fibrosis Stage 2-3 • Serial liver biopsy • 52 week Phase 3; 54 month outcomes
	Phase 3 MAESTRO-NAFLD-1 (presumed NASH) NCT04197479	Ongoing →				■ Treatment of NASH • *Safety, Lipids and NASH biomarker and imaging study* • *52 week* • *Enrollment of double-blind arms completed* • *Open label 100 mg arm; includes NASH cirrhotics*

MAESTRO Phase 3 trials provide a comprehensive data set to support efficacy and safety, consistent with regulatory requirements to support accelerated approval of resmetirom for treatment of patients with NASH with significant liver fibrosis

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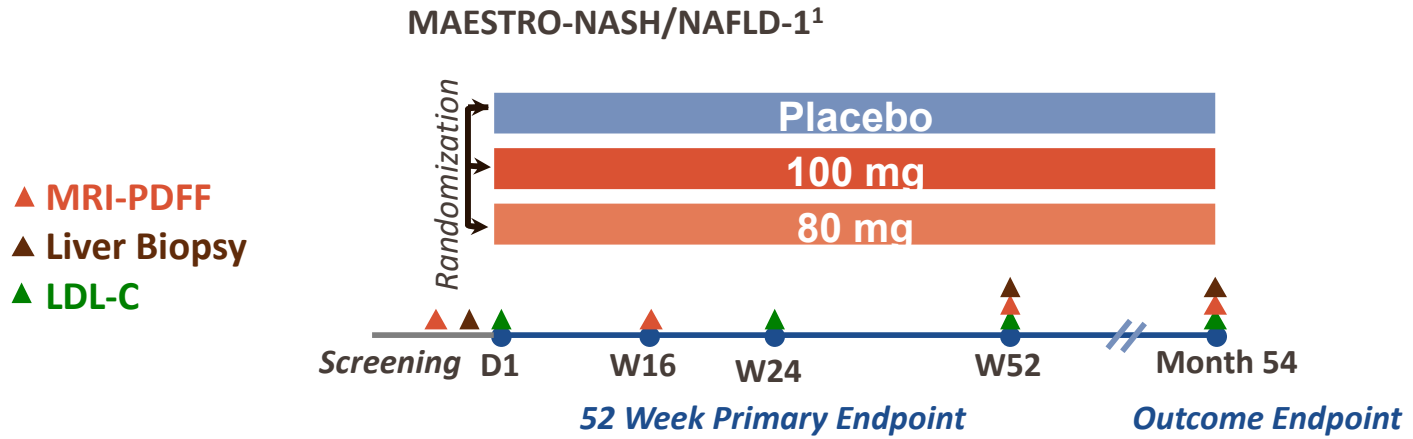
MAESTRO Phase 3 Program Study Design



- MAESTRO 52 Week Phase 3 trials, MAESTRO- NASH and MAESTRO-NAFLD-1 provide a comprehensive data set in more than 2000 NASH patients to support efficacy and safety of resmetirom
  - Consistent with regulatory requirements to support accelerated approval of resmetirom for treatment of patients with NASH and significant liver fibrosis
- Both trials employ non-invasive readouts that provide a framework for monitoring patients' treatment response to resmetirom
- Open-label arm of MAESTRO-NAFLD-1 provides ongoing data readouts, supporting safety and potential benefits of resmetirom treatment

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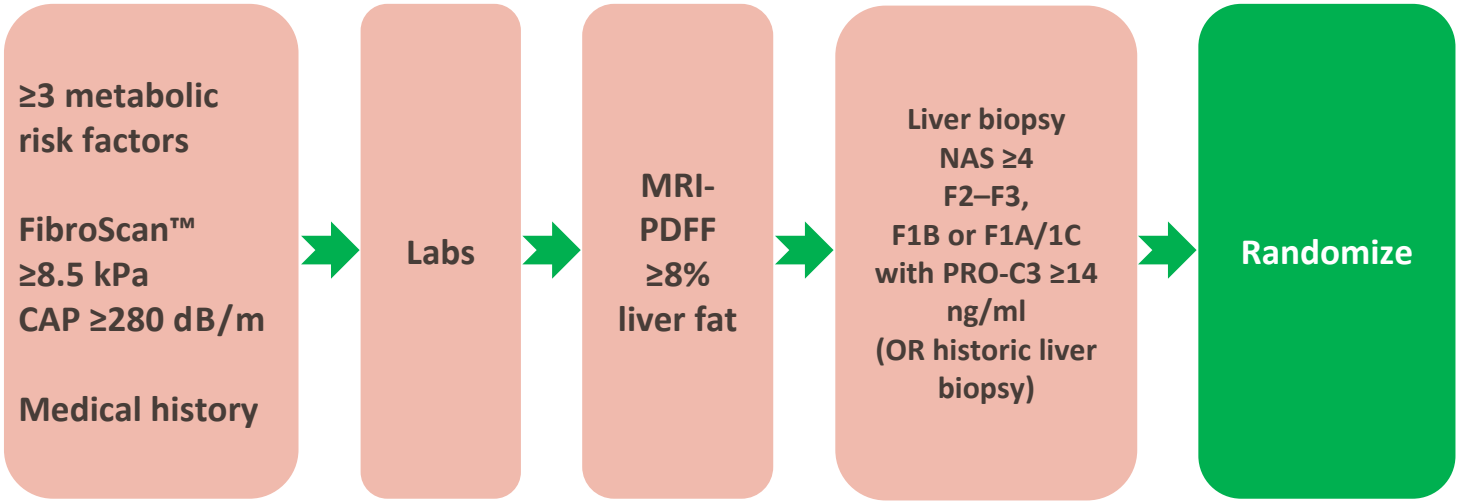
MAESTRO-NASH 8-Week Screening Algorithm

Risk factors for NASH
Age >50
BMI >30
Elevated liver enzymes
T2DM
Hypertension
Dyslipidemia
Metabolic syndrome
Historical FibroScan™ >8.5 kPa, CAP >280 dB/m

Enrolling patients in NASH fibrosis studies is particularly challenging because most patients at the time of screening do not have a definite diagnosis of NASH and their fibrosis stage is unknown

MAESTRO-NASH, 8 Week screening process[1]



Using this screening paradigm, more than 80% of screened patients have had definitive NASH with significant fibrosis on liver biopsy

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Diagnosing NASH and Monitoring Treatment Effects Non-invasively with Imaging

- In real life serial liver biopsies will be uncommon way to monitor NASH patients with significant liver fibrosis

- MRI-PDFF (Magnetic resonance-proton density fat fraction) is an accurate measure of liver fat (triglycerides)
  - In Phase 2, resmetirom was shown to potently reduced MRI-PDFF which correlates with NASH resolution and fibrosis reduction on liver biopsy

- In real life, additional imaging and biomarker non-invasive tests may be used to diagnosis NASH and monitor disease course and response to treatment
  - CAP (controlled attenuation parameter) is a less sensitive or specific correlate of liver fat content than MRI-PDFF, obtained using a FibroScan (VCTE), and office based procedure
  - Both MRE and FibroScan assessments of liver stiffness have been used to assess fibrosis stage
  - Other imaging tests are under development

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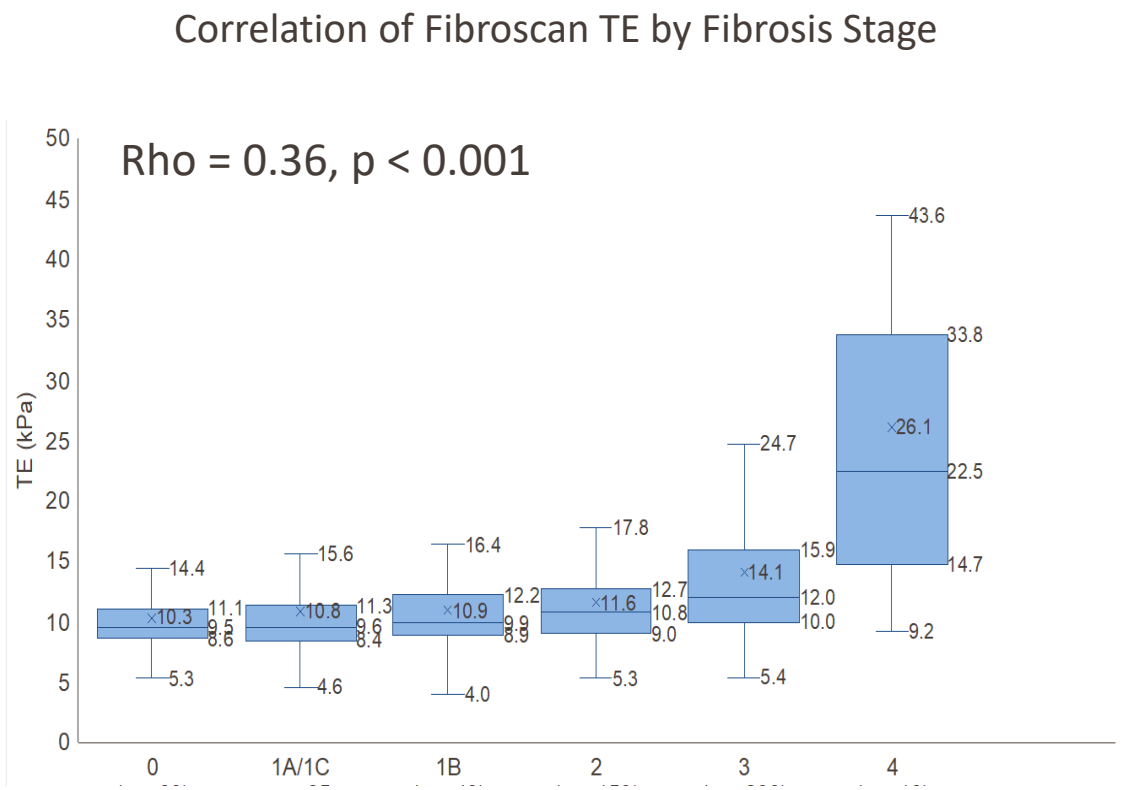
Correlation of Fibroscan TE by Fibrosis Stage in MAESTRO-NASH[1]



Screening data from the MAESTRO-NASH phase 3 trial[2]

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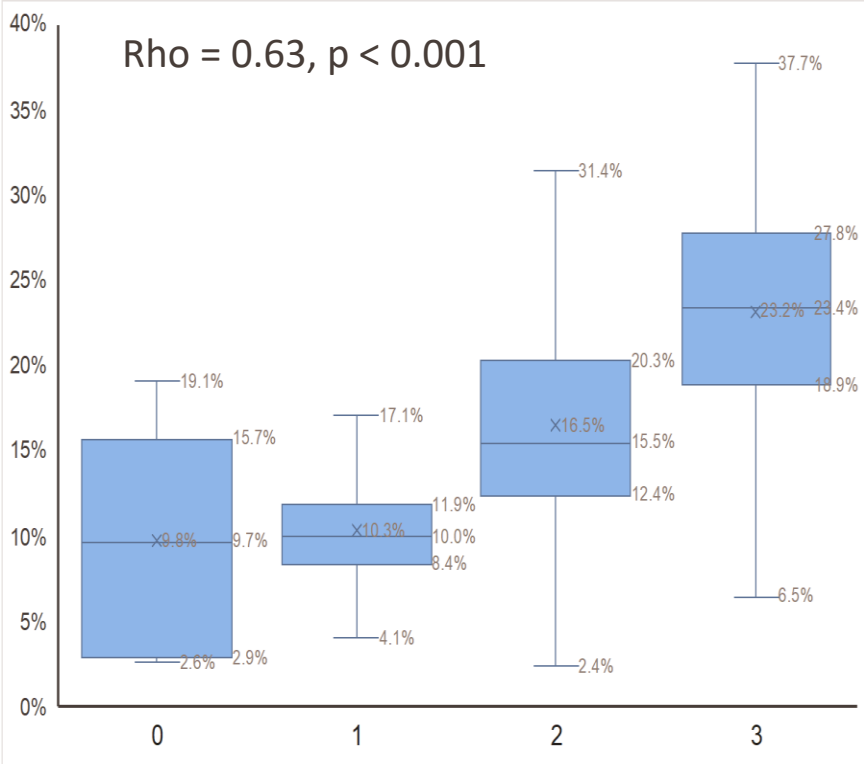
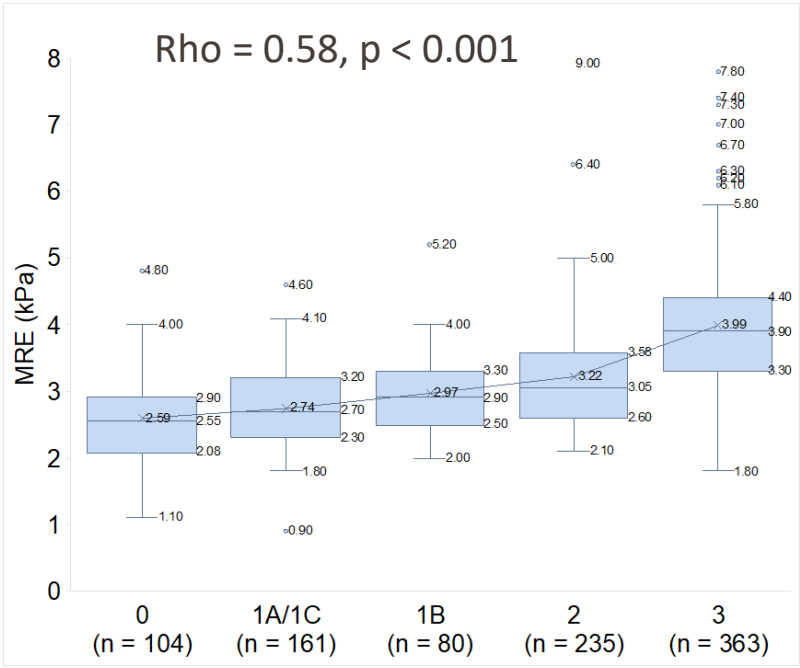
Relationship of MRI-PDFF and MRE to Screening Liver Biopsy[1]

Correlation of MRI-PDFF ≥8% with Steatosis on Liver Biopsy in MAESTRO-NASH



Correlation of MRE kPa by Fibrosis Stage in MAESTRO-NASH



Screening data from the MAESTRO-NASH phase 3 trial[2]

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Reduction in Fibrosis and Steatohepatitis Imaging and Biomarkers in a 52-week Resmetirom NASH Trial

Stephen A. Harrison[1], Naim Alkhouri[2], Rebecca A. Taub[3], Guy Neff[4], Seth J Baum[5], Ziad Younes[6] and Mustafa R. Bashir[7]

[1]Oxford United Kingdom, San Antonio, United States; [2]Arizona Liver Health, Phoenix, United States; [3]Rebecca A. Taub, Madrigal Pharmaceuticals, Conshohocken, United States; [4]Guy Neff, Covenant Research, LLC, Sarasota, United States; [5]Seth J Baum, Excel Medical Clinical Trials, Miami, United States; [6]Ziad Younes, Gastro-One, Memphis, United States; [7]Mustafa R Bashir, Department of Radiology, Duke University Medical Center, Durham, United States

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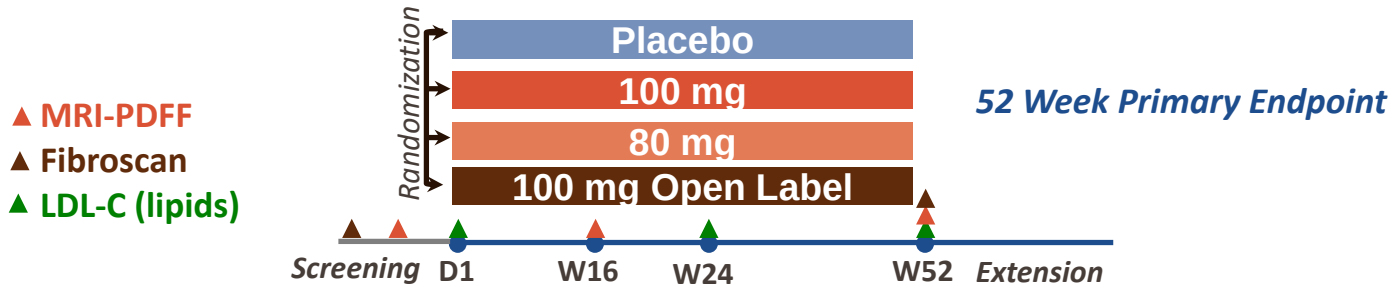
Phase 3 MAESTRO-NAFLD-1 (presumed NASH) Study Design: Randomized, Double-Blind, PBO Controlled with 100 mg Open Label Arm



Comparator/Arms

- 1:1:1:1 resmetirom 80, 100 mg , placebo, open label 100 mg
- ~1200 NASH patients enrolled in the USA (~65 sites)

Inclusion/Exclusion

- Requires 3 metabolic risk factors (Metabolic Syndrome)
- FibroScan (VCTE) kPa≥ 5.5, CAP≥280, except where eligible for MAESTRO-NASH; includes MAESTRO-NASH patients who screen fail at the biopsy stage
- ≥8 % liver fat on MRI-PDFF
- Open label arm, >100 patients
  - NASH patients on 100 mg resmetirom to assess non-invasive measure of safety and efficacy
  - Open-label treatment of special safety population, e.g. compensated cirrhosis

A "Real-life" NASH Study with Non-invasive Monitoring of Patient Response

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MAESTRO-NAFLD-1 Non-cirrhotic NASH Open Label Active 100 mg Treatment Arm

- An exploratory evaluation of safety, imaging and biomarkers was conducted in >150 patients enrolled in the open label 100 mg daily resmetirom dose active treatment arm of MAESTRO-NAFLD-1
- At the time of this presentation 115 patients had completed Week 52 including laboratory tests, safety analyses, MRI-PDFF, MRE, and FibroScan (VCTE)

MAESTRO-NAFLD-1 Endpoints

- Primary safety objective: to evaluate the safety and tolerability of once-daily, oral administration of 80 or 100 mg resmetirom versus matching placebo as measured by: Incidence of Adverse Events [Time Frame: 52 weeks]
- Key efficacy objectives: percent change from baseline in LDL-C; percent change from baseline in ApoB; percent change from baseline in hepatic fat fraction by MRI-PDFF; percent change from baseline in triglycerides; change in PRO-C3

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Baseline Characteristics, 100 mg Resmetirom Non-cirrhotic NASH Open Label Arm

MAESTRO-NAFLD-1 Baseline	mean	SD
Mean age, years (SD)	55.7	(11.3)
Male, n (%)	36	(29%)
Female, n (%)	87	(71%)
Hispanic/Latino, n (%)	32	(26%)
Mean Body weight (SD) (kg)	99.3	(19.8)
BMI mean (SD) (kg/m2)	36.2	(6.2)
Hypertension, n (%)	79	(64%)
Hypothyroid#, n (%)	48	(39%)
T2D, n (%)	50	(41%)
T2D Yrs since Dx mean (SD)	10.1	(7.5)
ASCVD score mean (SD)	11.1%	(11.7%)
Fibroscan TE mean (SD) (kPa)	7.4	(2.9)
Fibroscan CAP mean (SD)	341	(35.0)
MRI-PDFF mean (SD) (%FF)	18.0%	(6.9%)
MRE mean (SD) (kPa)	2.67	(0.73)
ELF mean (SD) (ng/ml)	9.3	(0.89)
HbA1c mean (SD) (%)	6.3	(1.0)
HOMA-IR mean (SD)	8.9	(8.9)
Statin use (n, %)	56	(46%)
GLP-1s (n, %)	15	(12.2%)
SGLT2s (n, %)	16	(13.0%)

Other lab parameters,	mean	SD
MELD	7.0	(1.6)
NAFLD fibrosis score	-1.2	(1.3)
Fib-4	0.99	(0.50)
Total Chol mean (SD) (mg/dL)	190.2	(49.2)
TG mean (SD) (mg/dL)	186.9	(85.5)
Lp(a) mean (SD) (nmol/L)	46.1	(64.3)
ApoB mean (SD) (mg/dL)	102.9	(29.6)
LDL-C mean (SD) (mg/dL)	117.7	(42.5)
HDL-C mean (SD) (mg/dL)	44.2	(11.9)
ALT (IU/L)	36.6	(23.7)
AST (IU/L)	25.5	(12.4)
GGT (IU/L)	44.1	(46.5)
CK (IU/L)	121.2	(111.6)
ALP (IU/L)	83.6	(26.5)
Total bilirubin (mg/dL)	0.55	(0.21)
Direct bilirubin (mg/dL)	0.10	(0.04)
Platelet count	263	(67)
Albumin (g/dL)	4.3	(0.3)
INR	1.1	(0.3)
CDT (%)	1.62	(0.23)

- Demographics include
  - Mean age 55.7,
  - female 71%,
  - BMI 36.2,
  - diabetes 41%,
  - hypertension 64%,
  - dyslipidemia >70%,
  - hypothyroid 41%
  - mean ASCVD score 11.1%
- FibroScan (kPa 7.4) and mean MRI-PDFF 18%
  - Comparatively, MAESTRO-NASH baseline FibroScan kPa mean is 13.0

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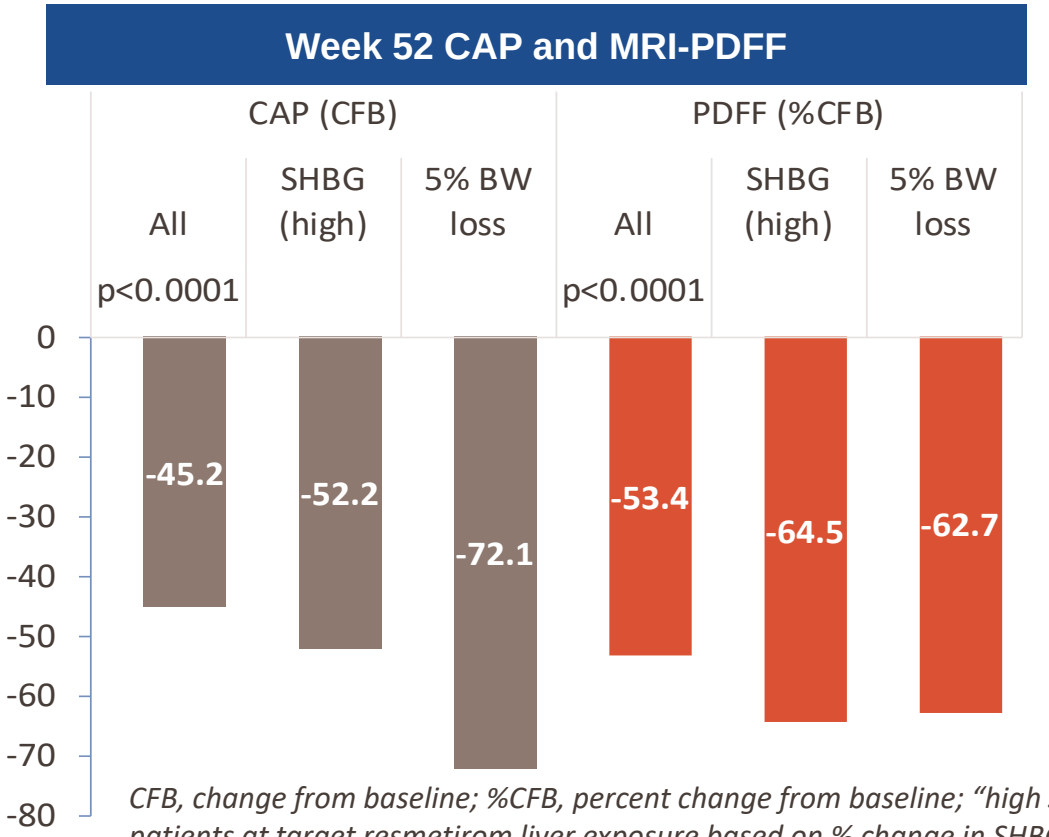
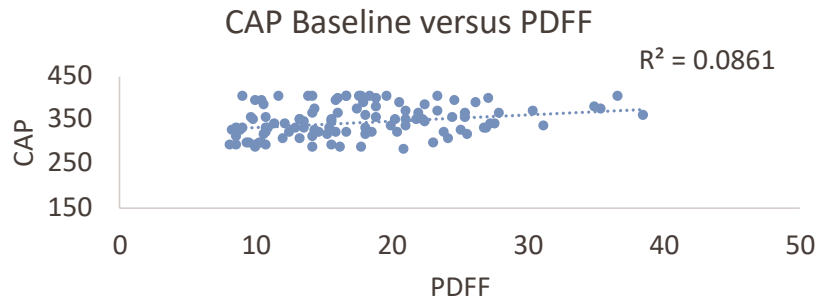
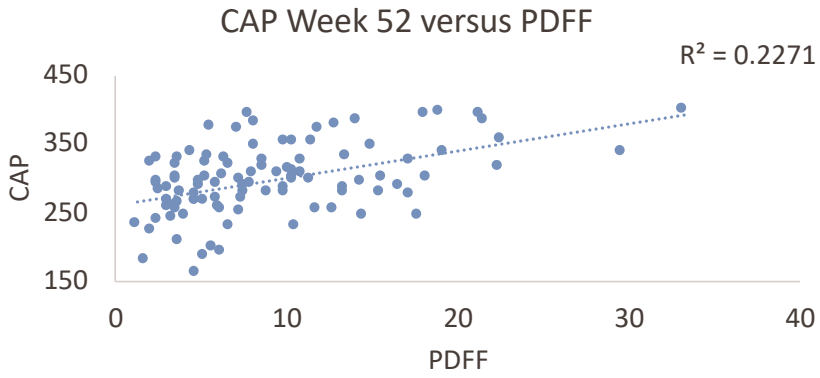
Resmetirom-Mediated Reduction in Liver Fat as Assessed by MRI-PDFF and CAP







CFB, change from baseline; %CFB, percent change from baseline; "high SHBG", majority of patients at target resmetirom liver exposure based on % change in SHBG

- Serial MRI-PDFF measurements and FibroScan with CAP, both measures of liver fat content in 115 patients at Week 52
- The correlation between baseline MRI-PDFF and CAP was weak; relative inability of CAP to accurately quantitate steatosis
- Resmetirom potently reduced both CAP and MRI-PDFF at Week 52

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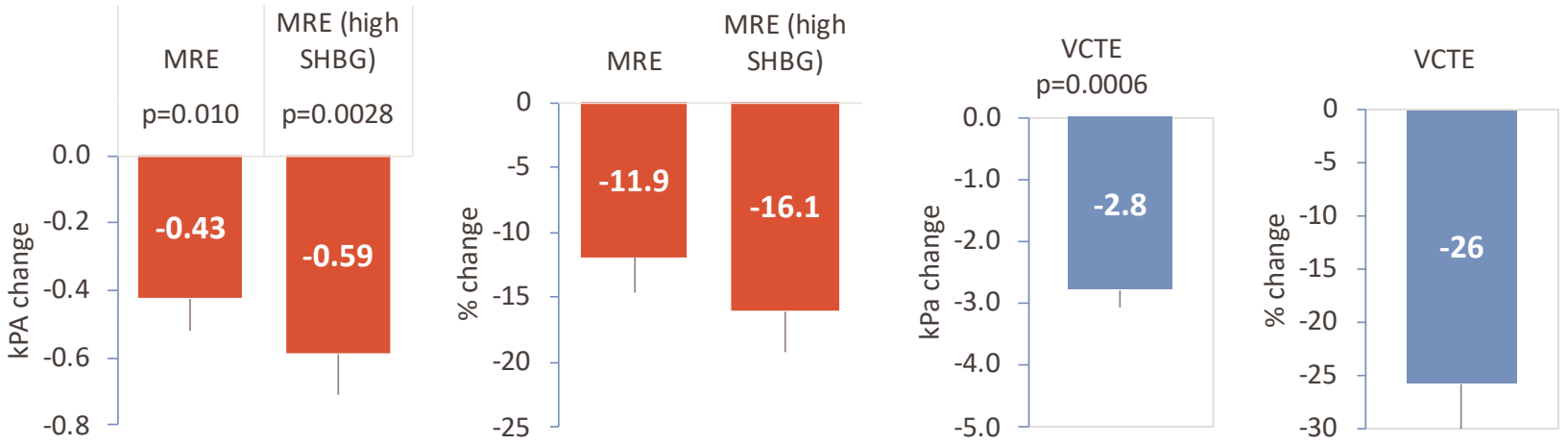
Improvements in Fibrosis Imaging and Biomarkers at Week 52

Week 52 MRE and FibroScan (kPa)



	Baseline	Week 52	
		Change	p-value
CK-18 (M30)	637	-300	<0.0001
ELF	10.6	-0.4	0.03
Reverse T3	17.6	-3.6	<0.0001
	Parameter	Baseline	Week 52
FibroScan (kPa)	BL >=7.4	9.8	7.0
MRE (kPa)	BL>=2.9	3.5	3.1

- Reductions in kPa on FibroScan and MRE were observed
  - Approximately 50% of patients had a 15% reduction in MRE (kPa) and/or 25% reduction in FibroScan (VCTE) kPa
  - Targets hypothesized to reflect histologic fibrosis progression[1]
- Serum fibrosis/inflammation biomarkers showed reductions over the time-course of the study and at Week 52
- Change from baseline in non-invasive fibrosis imaging and biomarkers may reflect change in inflammation and/or fibrosis on liver biopsy at Week 52

CK-18, cytokeratin 18; ; ELF, Enhanced liver fibrosis (>=10 BL);; Reverse T3, reverse triiodothyronine, kPa, kilopascal; VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; BL, baseline

[1] Hepatology, VOL . 71, NO. 3, 2020; Hepatology, VOL . 73, NO. 2, 2021

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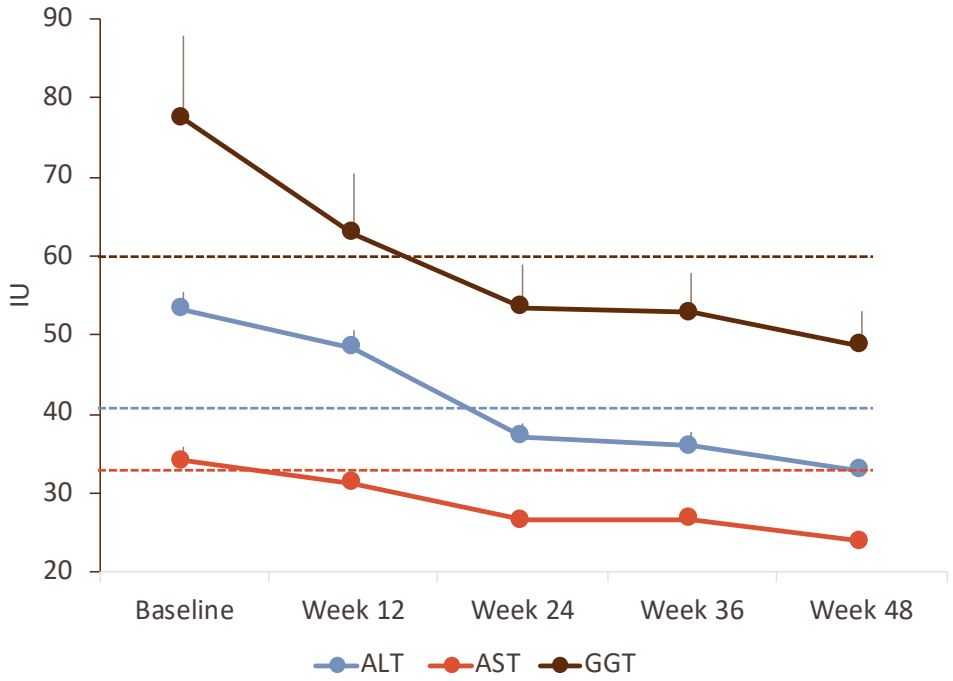
Resmetirom-Mediated Reductions in Liver Enzymes



Week 48	CFB	%CFB	p-value
ALT	-20.36	-33.04	<0.0001
AST	-10.19	-21.50	0.0003
GGT	-28.52	-19.83	0.015

- Liver enzymes are minimally elevated in most NASH patients
- Patients with mild to moderate ALT or GGT elevations at baseline reduced their liver enzymes on resmetirom treatment during the study

Upper limit of normal range, dotted line; Population was patients with baseline ALT>30 IU for ALT and AST; GGT>=30 for GGT

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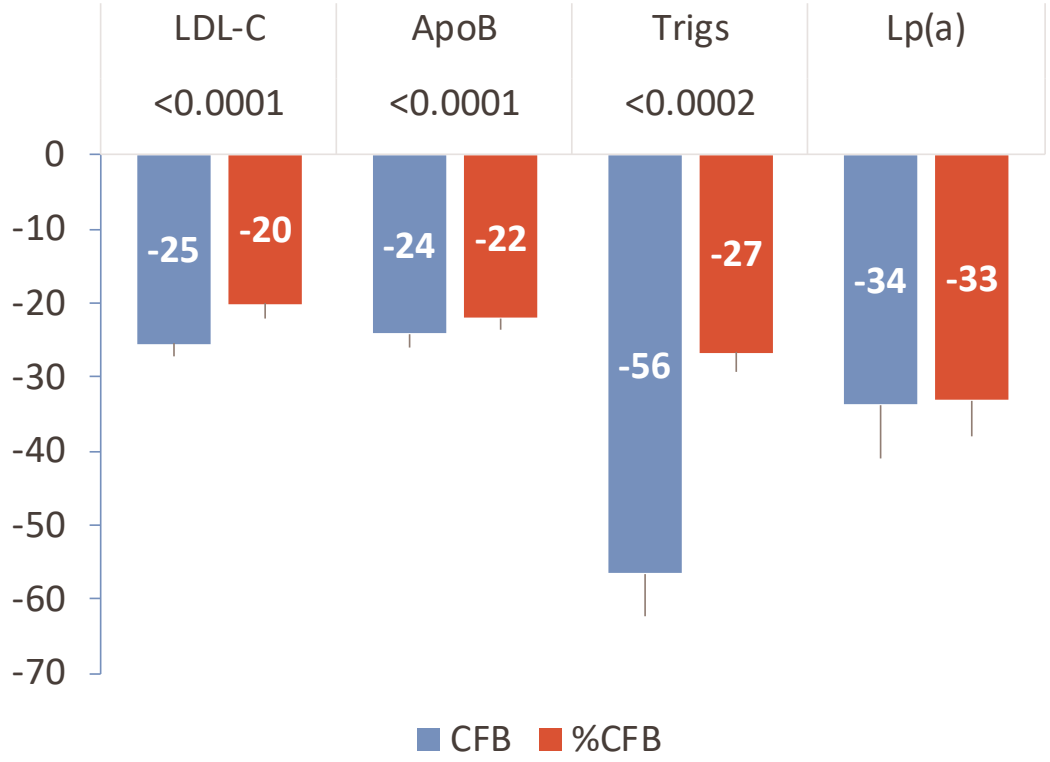
Safety Summary and CV Effects

- Resmetirom at 100 mg per day was well-tolerated
  - 95% completion rate; 1 withdrawal for AE
  - GI AEs, generally mild AE, increased stool frequency in ~10% over historic placebo rates, not leading to study discontinuation, observed at the beginning of therapy
  - 6.8% with COVID AE; COVID, most common SAE; no other SAE more than 1 occurrence, none related, total non-COVID SAEs 3.4%
  - All other AEs <5%
  - No central thyroid axis changes or adverse effects on vital signs
- Resmetirom reduced markers of cardiovascular risk
  - CV disease is increased in NASH patients
  - Reduced LDL-C, ApoB, triglycerides and lipoprotein (a), key secondary endpoints in MAESTRO studies
  - Small decrease in BP may reflect metabolic syndrome improvement



	CFB	SE	P-value
Blood pressure (mm Hg)			
Systolic	-5.3	1.4	0.0093
Diastolic	-3.7	0.89	0.0033
Body weight (kg)[1]	-1.5	0.50	NS

CFB, change from baseline [1]21% lost >=5% BW; 9% increased BW>=5%

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Conclusions: MAESTRO-NASH-NAFLD-1 100mg Open Label

- In this 52 week Phase 3 open label study of resmetirom, a once-a-day oral medication, noninvasively identified NASH patients treated with 100 mg per day of resmetirom for up to 52 weeks demonstrated rapid and sustained reduction in
  1. Hepatic fat
  2. Fibrosis as assessed by ELF, MRE and FibroScan
  3. Liver cell injury and inflammatory biomarkers
  4. LDL and atherogenic lipids

- Resmetirom is well-tolerated at 100 mg per day

- Limitations of the study include relatively early patient population, absence of a placebo control group

- This study highlights the potential use of non-invasive tests to diagnose NASH and monitor individual NASH patient response to resmetirom treatment

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Resmetirom Treatment of NASH-Cirrhosis
MAESTRO-NAFLD-1 52 Week Open Label active treatment arm

EASL Poster #849

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52 Week NASH-Cirrhosis Open Label Active Resmetirom Treatment Arm

For the open label NASH cirrhosis active treatment arm:

- Eligible patients must have compensated NASH cirrhosis diagnosed by liver biopsy showing NASH with F4 stage fibrosis (either historic or recent biopsy) or a historic biopsy with NASH F2-F3 fibrosis with subsequent progression to NASH cirrhosis as diagnosed by an expert hepatologist/gastroenterologist.
  - If no liver biopsy has been obtained, clinical evidence of compensated NASH cirrhosis as determined by a gastroenterologist/hepatologist
- Cirrhosis must be well-compensated with no history of decompensation Child–Pugh A (5–6)
- All cirrhotic patients receive active treatment. Starting dose in NASH cirrhotic patients is 80 mg resmetirom and can be adjusted to 100 mg based on a Week 2 PK sample
  - In Phase 1 studies, PK in NASH cirrhotics compared to normal NASH showed that at 80 and 100 mg dose, there is no difference in resmetirom exposures. 100 mg represents a 40-50% increase in exposure over 80 mg in both populations
- Other than the addition of a Week 2 visit, the NASH cirrhotic 52 week protocol is identical to MAESTRO-NAFLD-1 non-cirrhotic protocol

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NASH-Cirrhosis Baseline

MAESTRO-NAFLD-1 NASH Cirrhosis Baseline Characteristics		
N =	105	
Mean age, years (SD)	62.7	(9.0)
Male, n (%)	39	(36%)
Female, n (%)	69	(64%)
Hispanic/Latino, n (%)	26	(24%)
Mean Body weight (SD) (kg)	98.2	(24.5)
BMI mean (SD) (kg/m2)	35.4	(7.4)
MELD	8	(1.9)
MRI-PDFF mean (SD) (%FF)	8.1%	(5.0%)
MRE mean (SD) (kPa)	5.74	(2.09)
Historical Biopsy if available (n)	67	
Fibrosis stage 4 (n, %)	53	(79.1%)
Fibrosis stage 3 (n, %)	9	(13.4%)
Hypertension, n (%)	83	(77%)
Hypothyroid#, n (%)	35	(32.4%)
T2D, n (%)	76	(70%)
T2D Yrs since diagnosis mean (SD)	12.7	(8.5)
Documented ASCVD@, n	11	(10.2%)
ASCVD score mean (SD)	16.1%	(0.1)
Fibroscan TE mean (SD) (kPa)	24.6	(14.9)
Fibroscan CAP mean (SD)	318	(58.9)
HbA1c mean (SD) (%)	6.4	(1.0)
HOMA-IR mean (SD)	10.5	(7.2)
Statin use (n, %)	55	(50.9%)
>75ug (n, %)	23	(21.3%)
GLP-1s (n, %)	25	(23.1%)
SGLT2s (n, %)	26	(24.1%)

Other lab parameters, mean (SD)		
NAFLD fibrosis score	1.1	(1.6)
Fib-4	2.9	(1.7)
ELF	10.8	-(1.2)
Total bilirubin mean (SD) (mg/dL)	0.9	(0.5)
Direct bilirubin mean (SD) (mg/dL)	0.2	(0.1)
Platelet count mean (SD)	158	(60.7)
Albumin mean (SD) (g/dL)	4.2	(0.4)
INR mean (SD)	1.2	(0.1)
Total Cholesterol mean (SD) (mg/dL)	169	(44.3)
TG mean (SD) (mg/dL)	165	(119.8)
Lp(a) mean (SD) (nmol/L)	44.4	(61.7)
ApoB mean (SD) (mg/dL)	85.1	(24.3)
LDL-C mean (SD) (mg/dL)	95.5	(34.0)
HDL-C mean (SD) (mg/dL)	47.5	(16.7)
ALT (IU/L)	40.3	(26.9)
AST (IU/L)	39.4	(24.9)
GGT (IU/L)	102	(88.8)
CK (IU/L)	101	(65.4)
ALP (IU/L)	102	(52.6)
MCV (fL)	91	(6.3)
CDT (%)	1.7	(0.3)

- Demographics include
  - Mean age 62.7
  - female 64%,
  - BMI 35.4
  - diabetes 70%
  - hypertension 77%
  - hypothyroid 32%
  - mean ASCVD score 16.1%
- FibroScan (kPa 24.6), MRE (5.74) consistent with F4 fibrosis

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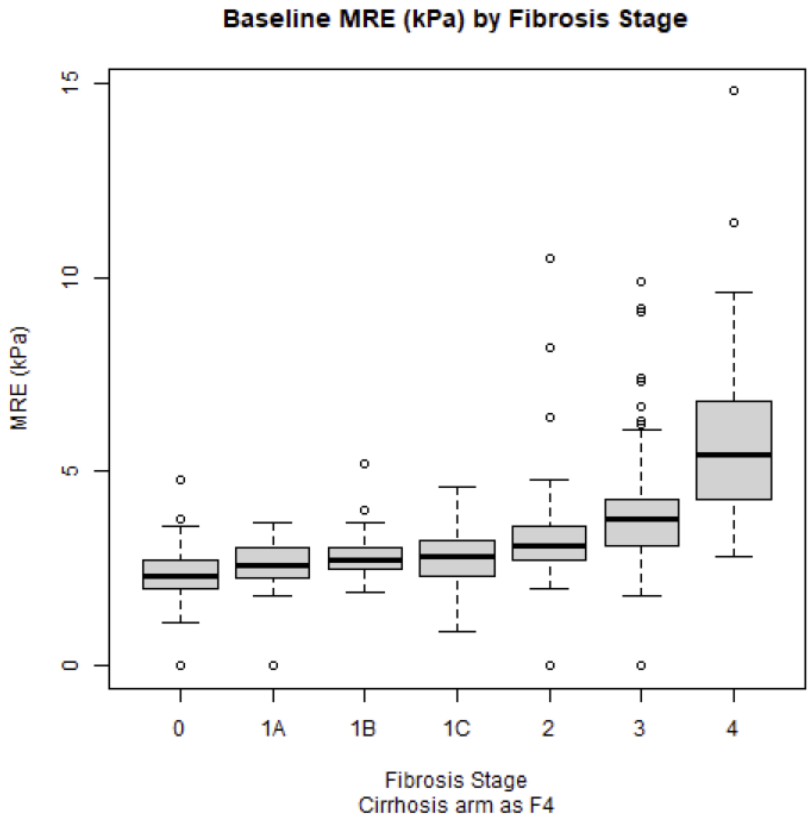
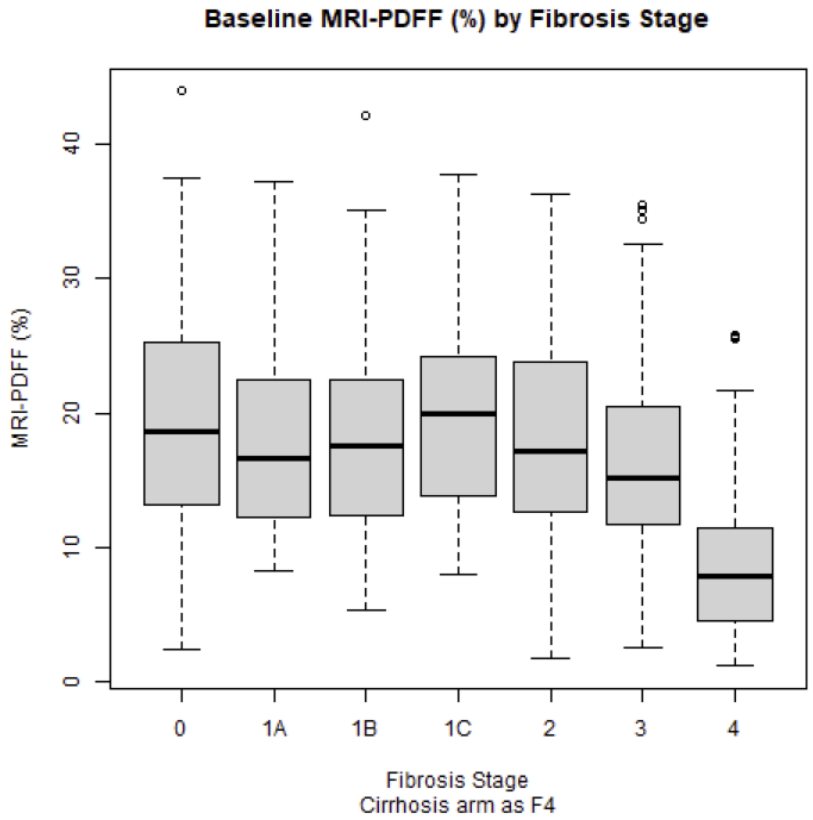
Baseline MRI-PDFF and MRE in NASH Cirrhotics Compared with Non-Cirrhotic NASH

- **MRE: Rho = 0.6, highly predictive of F4 compared with all lower stages of fibrosis**
- Significant decrease in PDFF in F4 compared with earlier fibrosis stages





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Comparison of Cirrhosis Parameters According to Baseline MRI-PDFF

- NASH cirrhotic patients with lower MRI-PDFF <=5% at baseline had more progressed cirrhosis based on several parameters of progression

Baseline Parameters	Gp 1, PDFF <=5%	Gp 2, PDFF >5%, <8%	Gp 3, PDFF >=8%	P-value (diff between Gp1 and Gp3)
	N=31	N=28	N=40	
PDFF	3.8%	6.8%	12.8%	p<0.0001
Fib-4	3.7	2.7	2.5	0.006
CAP	299.0	316.0	339.0	0.004
Fibroscan TE (kPa)	27.4	24.9	23.6	NS
MRE	6.1	5.8	5.5	NS
ALT (IU)	32.0	34.2	51.8	0.005
AST (IU)	38.7	33.7	44.6	NS
ELF	11.1	10.8	10.7	0.180
Markers of Cirrhosis Progression				
MELD	8.8	8.0	7.5	0.005
INR	1.2	1.2	1.1	0.030
Bilirubin (mg/dL)	1.08	0.86	0.71	0.004
Platelets	133	152	175	0.002
Albumin	4.0	4.2	4.3	0.030

Gp = group

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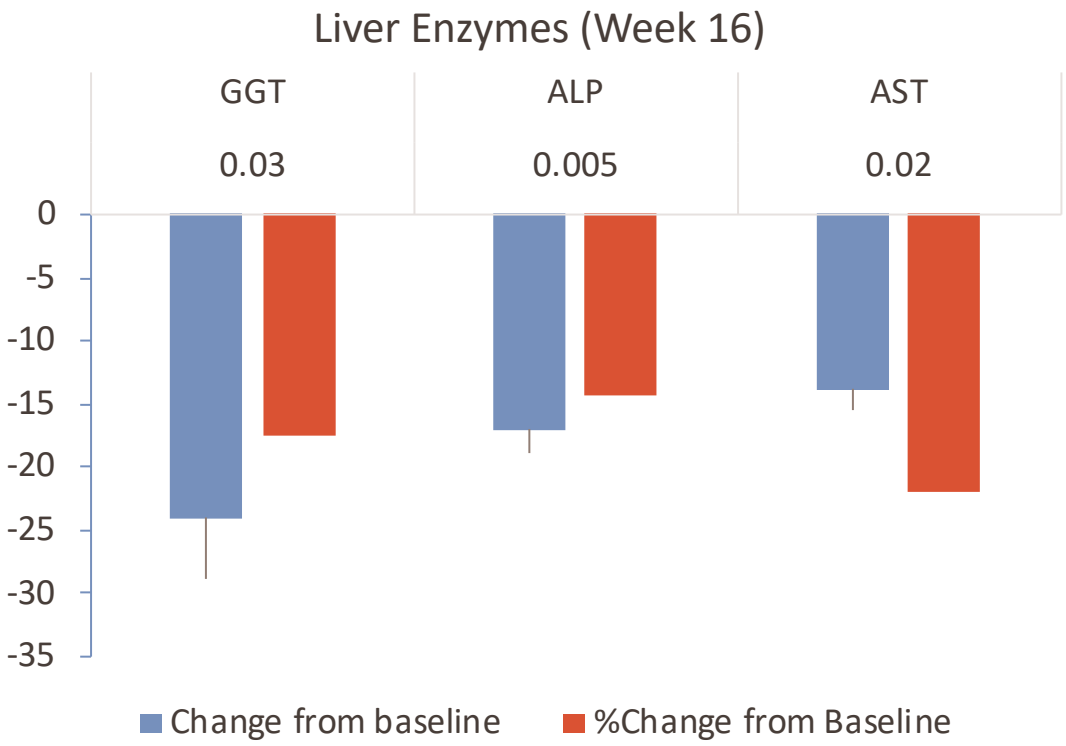
Early Responses to Resmetirom Treatment in NASH Cirrhosis Patients

16 Week MRI-PDFF and MRE	Value	SD	p-value
MRI-PDFF	-34%	(-29.7)	0.00026
≥30% Responder (%)	60%		
MRE (Baseline >=3.5) (kPa)	-0.5	(-1.1)	0.08
%≥15% reduction responder (%)	35%		

PDFF only assessed in group with >=8% PDFF at baseline

Fibrosis Markers[1]	Value	SD	p-value
M30	-126.00	349.00	0.08
ELF	-0.26	0.53	0.1
P3NP	-2.90	4.00	0.02
TIMP	-27.00	48.00	0.05
Reverse T3	-21%	21.70	<0.0001

[1]Patients (n=28) in groups 2-3 who reached week 24



Assessed at Week 16

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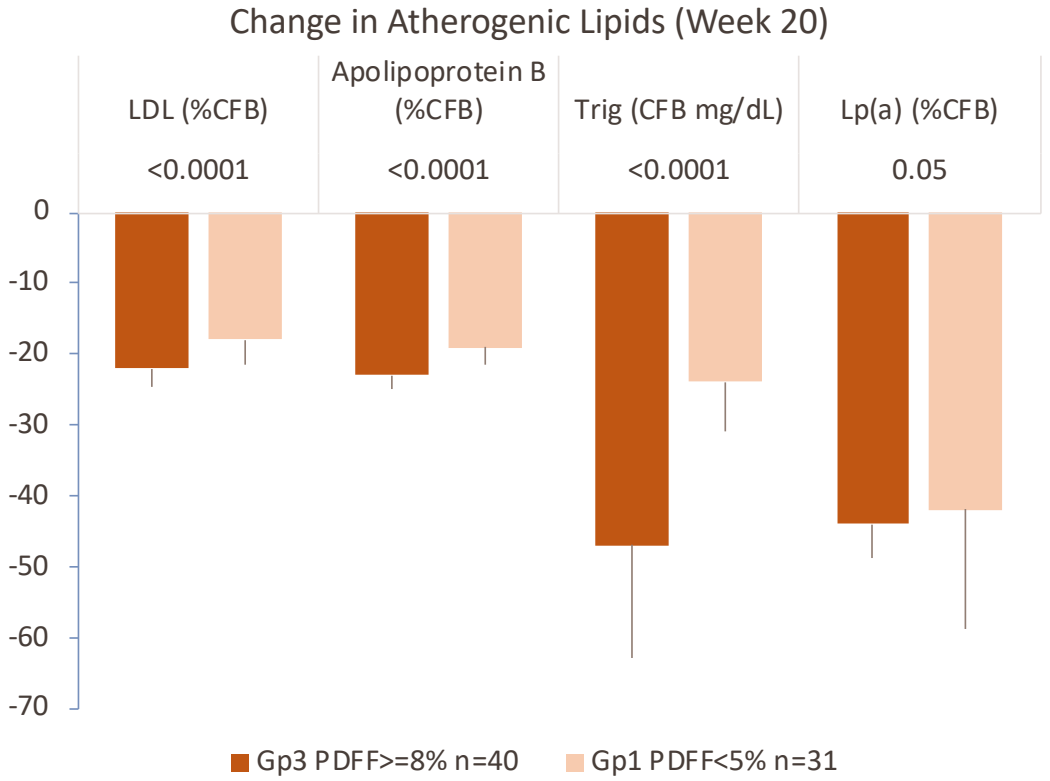
Cardiovascular Risk Factors and Safety

- Lipids assessed as a comparison between group with elevated liver fat compared with low liver fat (more progressed)
  - Statistically significant reductions similar to non-cirrhotic NASH
  - No changes in vital signs, or differences between groups
- No differences in safety parameters between severity groups or compared with non-cirrhotic NASH were noted
  - Most common AE, ~10% mild, intermittent loose stools at initial therapy
  - No other Aes were >5%
  - SAE, 5% of patients, none related, all single occurrences



	Gp1 PDFF<5%	Gp3 PDFF>=8%	P-value (all)
Blood pressure			
systolic	-8.3	-3.0	0.028
diastolic	-3.3	-1.6	0.14
Body weight	-1.1	-1.2	NS

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Conclusions: MAESTRO-NASH–NAFLD-1 Cirrhotic Open Label Arm

- NASH cirrhotics have significantly higher MRE and lower PDFF than non-cirrhotic NASH patients. NASH cirrhotics with lower baseline PDFF may represent a more advanced subtype
- Resmetirom appeared to be safe in well-compensated NASH cirrhotic patients
- Resmetirom reduced MRI-PDFF and LDL cholesterol and other atherogenic lipids in NASH cirrhotic patients
- Limitations of the study include early stage of the study and lack of placebo control group
- Early trends to show decreases in fibrosis biomarkers and imaging will be followed by long term data at 52 weeks in NASH cirrhotic patients

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Summary

- The MAESTRO Studies Provide
  - Insights on the utilization of non-invasive technologies to identify patients and monitor treatment
  - Evidence of fibrosis stage reduction as assessed by ELF, MRE and fibroscan
  - A comprehensive assessment of NASH cirrhosis patients utilizing non-invasive measures

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Thank You!

Stephen Harrison

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