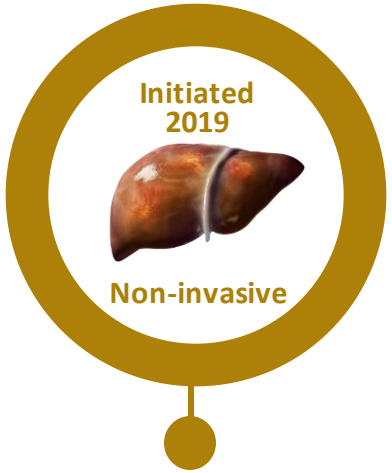
Madrigal Pharmaceuticals

Liver Forum 2024

Taub

NASDAQ: MDGL

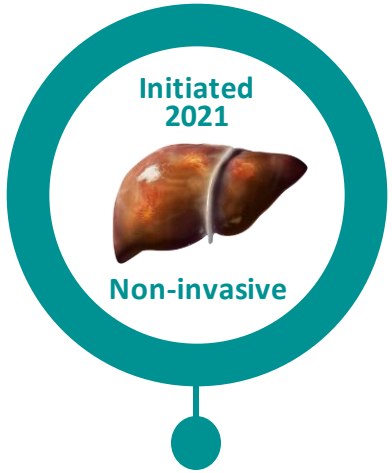
Phase 3 Resmetirom Clinical Development Program Spanning Disease Spectrum



MAESTRO NAFLD-1

N>1200 NAFLD patients
Safety & tolerability
over 52 weeks

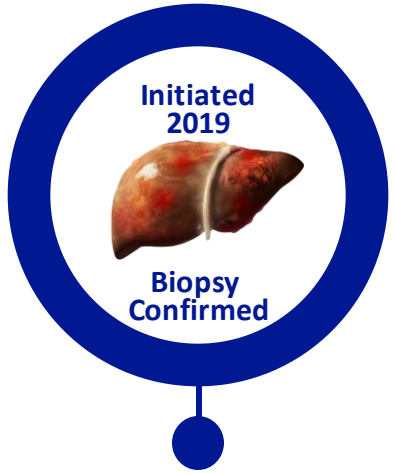
N=180 well-compensated NASH cirrhosis patients
Long-term Safety



MAESTRO NAFLD-OLE

(open label extension of MAESTRO NAFLD-1)

N>700 NAFLD patients
Safety & tolerability
>52 weeks



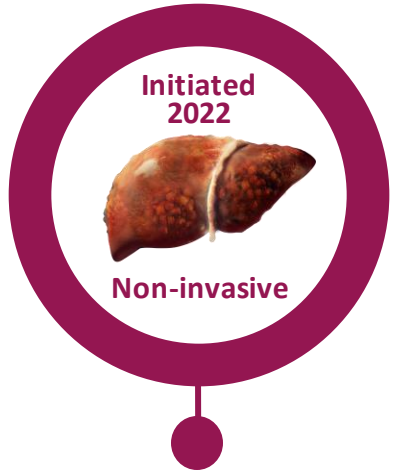
MAESTRO NASH

NASH F1B-F2-F3

Pivotal

N=966 NASH patients
NASH resolution
or fibrosis improvement
at Week 52

54-month ongoing clinical outcomes study



MAESTRO NASH OUTCOMES

N~700 well compensated NASH cirrhosis patients
Progression to decompensated cirrhosis

Supportive

Confirmatory

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Rezdiffra Prescribing Information: Best-Case Scenario Indication

INDICATIONS AND USAGE

INDICATIONS AND USAGE ----------
REZDIFFRA is a thyroid hormone receptor beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).
This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

- NASH with moderate to advanced liver fibrosis (consistent with F2/F3)
- No biopsy requirement
- No contraindications; no black box warnings

Rezdiffra Indication: Clearly States Where Rezdiffra Should Not Be Used

INDICATIONS AND USAGE[1]

REZDIFFRA is a thyroid hormone receptor beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitations of Use
Avoid use of REZDIFFRA in patients with decompensated cirrhosis

Avoid use of Rezdiffra in patients with decompensated cirrhosis

1. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024.

Rezdiffra Prescribing Information: Dosage and Administration

---------- DOSAGE AND ADMINISTRATION • The recommended dosage of REZDIFFRA is based on actual body weight. For patients weighing:

- <100 kg, the recommended dosage is 80 mg orally once daily.
- ≥100 kg, the recommended dosage is 100 mg orally once daily.

Administer REZDIFFRA with or without food. (2.1)

---------- DOSAGE FORMS AND STRENGTHS

Tablets: 60 mg, 80 mg, or 100 mg (3)

- Simple body weight as a determination of dose
- Based on optimizing exposure to resmetirom since body weight is the single feature that predicts exposure in patients with NASH
- Efficacy at each dose according to body weight cutoffs of 100 kg (220 pounds) is included in Table S10 of NEJM

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Rezdiffra Sets the Safety Bar in NASH

Common Adverse Reactions Reported with Rezdiffra[1,2]

Adverse Reaction	Placebo	Rezdiffra 80 mg Once Daily	Rezdiffra 100 mg Once Daily
	N=294	N=298	N=296
	n (EAIR[1])	n (EAIR[1])	n (EAIR[1])
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18(4)	24(6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

- Most frequent AEs were GI-related and generally transient with resolution over time
- Diarrhea lasted on average 2-3 weeks often characterized as loose stools or worsening of underlying diarrhea

Pruritus, itchiness of skin; **AEs,** adverse events; **EAIR,** exposure-adjusted incidence rate; **PY,** person-years.

1. The EAIR per 100 PY can be interpreted as an estimated number of first occurrences of the adverse reaction of interest if 100 patients are treated for one year. 2. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024.

Rezdiffra Prescribing Information: Clinical Studies

Demographic and baseline characteristics were balanced between treatment and placebo groups. Overall, the median (Q1 to Q3) age of patients at baseline was 58 (51 to 65) years, 56% were female, 21% were Hispanic, 89% were White, 3% were Asian, and 2% were Black or African American. Median (Q1 to Q3) body mass index (BMI) was 35 (31 to 40) kg/m^2 and median (Q1 to Q3) body weight was 99 (85 to 114) kg. Baseline characteristics are presented in Table 7.

Table 7. Baseline Characteristics in Patients with Stage 2 to Stage 3 Fibrosis in Trial 1

Characteristic	Overall N=888
Fibrosis stage, n (%)	
F2	328 (37)
F3	560 (63)
Type 2 Diabetes, n (%)	608 (69)
Hypertension, n (%)	700 (79)
Dyslipidemia, n (%)	633 (71)
Statin use, n (%)	434 (49)
Thyroxine use, n (%)	124 (14)
Vibration-controlled Transient Elastography (VCTE) (kPa), Median (Q1, Q3)[a, b]	11.8 (10, 15)
Controlled attenuation parameter (CAP) (Db/M), Median (Q1, Q3)[a]	349 (320, 378)
Fibrosis Index Based on 4 Factors (FIB-4), Median (Q1, Q3)[a]	1.3 (1, 1.8)
Enhanced Liver Fibrosis (ELF), Median (Q1, Q3)[a]	9.7 (9.2, 10.4)

[a] Less than 5% missingness in these variables is omitted.
[b] kPa = kilopascal; Db/M = decibels per meter

- Helpful information emphasizes the metabolic characteristics of NASH patients: BMI, diabetes, hypertension, dyslipidemia
- Provides median values for important tests that are expected to be available to prescribers including liver stiffness, CAP, and ELF
- Demonstrates that FIB-4 is not that useful

Rezdiffra Label: Strong Clinical Efficacy on Fibrosis Improvement and NASH Resolution

Clinical Efficacy in Rezdiffra Label[1]

	Placebo N=294	80 mg N=298	100 mg N=296
	Improvement in liver fibrosis and no worsening of steatohepatitis		
Response rate, Pathologist A (%)	15	23	28
Difference in response rate vs. placebo (95% CI)		8 (2, 14)	13 (7, 20)
Response rate, Pathologist B (%)	13	23	24
Difference in response rate vs. placebo (95% CI)		11 (5, 17)	11 (5, 7)
	Resolution of steatohepatitis and no worsening of liver fibrosis		
Response rate, Pathologist A (%)	13	27	36
Difference in response rate vs. placebo (95% CI)		14 (8, 20)	23 (16, 30)
Response rate, Pathologist B (%)	9	26	24
Difference in response rate vs. placebo (95% CI)		17 (11, 23)	15 (9, 21)

From Rezdiffra Label[1]

- *Two pathologists, Pathologist A and Pathologist B, independently read the liver biopsies for each patient.*
  - *Both the 80 mg once daily and the 100 mg once daily dosages of REZDIFFRA **demonstrated improvement on these histopathology endpoints** at Month 12 compared to placebo.*
- *In a statistical analysis incorporating both pathologists' independent readings, REZDIFFRA **achieved statistical significance on both histopathology endpoints for both doses**.*

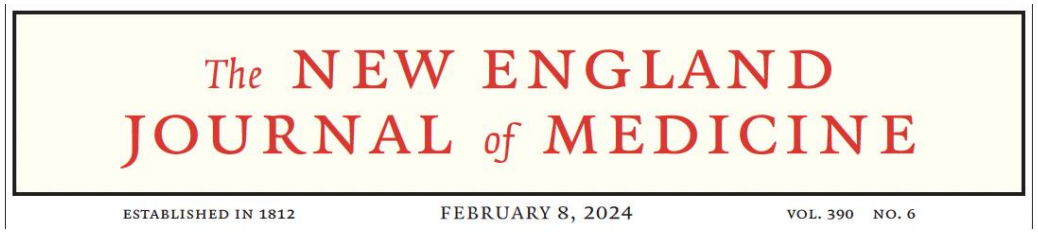
1. Rezdiffra prescribing information. West Conshohocken, PA: Madrigal Pharmaceuticals, Inc.; 2024. Label: The 888 population was based on patients determined to be F2/F3 based on scoring of the baseline liver biopsy by a central reviewer at the time of randomization into the study. FDA Endpoints: Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4. Resolution of steatohepatitis was defined as a score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis. No worsening of steatohepatitis was defined as no increase in score for ballooning, inflammation, or steatosis. Estimated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). 95% stratified Newcombe confidence intervals (CIs) are provided. Patients with missing liver biopsy at Month 12 are considered a non-responder.

Consistent Efficacy Across All Endpoints, Doses, Patient Populations

	Label F2/F3 Population[1,2]						Madrigal F1B/F2/F3 Population[1,2]					
	MAESTRO-NASH *Label Endpoints*			MAESTRO-NASH *Prespecified Endpoints*			MAESTRO-NASH *Label Endpoints*			MAESTRO-NASH *Prespecified Endpoints (NEJM)*		
	Placebo	*80 mg*	*100 mg*	*Placebo*	*80 mg*	*100 mg*	*Placebo*	*80 mg*	*100 mg*	*Placebo*	*80 mg*	*100 mg*
Fibrosis Improvement	14%	23% p < 0.001	26% p < 0.001	16%	25% p = 0.002	27% p < 0.001	12%	23% p < 0.001	24% p < 0.001	14%	24% p < 0.001	26% p < 0.001
NASH Resolution	11%	25% p < 0.001	30% p < 0.001	9%	24% p < 0.001	29% p < 0.001	12%	27% p < 0.001	32% p < 0.001	10%	26% p < 0.001	30% p < 0.001
Number of Patients	888			888			966			966		

1. Label: The 888 population was based on patients determined to be F2/F3 based on scoring of the baseline liver biopsy by a central reviewer at the time of randomization into the study. Label Endpoints: Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4. Resolution of steatohepatitis was defined as a score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis. No worsening of steatohepatitis was defined as no increase in score for ballooning, inflammation, or steatosis. Estimated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). 95% stratified Newcombe confidence intervals (CIs) are provided. Patients with missing liver biopsy at Month 12 are considered a non-responder.
2. MADRIGAL: 966 population of F1B, F2, F3 patients was based on the primary efficacy read of baseline slides that was conducted by Path A and Path B near the Week 52 completion date. Madrigal Endpoints: Resolution of NASH Resolution of steatohepatitis was defined as a score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis with no worsening of fibrosis stage and at least a 2-point reduction in NAS. Fibrosis improvement, at least a 1 stage improvement in fibrosis with no worsening of NAS. NAS, NAFLD Activity Score, the unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2); thus ranging from 0 to 8.

Non-invasive Data Provided in Feb 8th 2024 NEJM



The NEW ENGLAND JOURNAL of MEDICINE

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A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

Sparse Non-invasive Data in Label

Measurement (study week)	LS Mean %CFB (SE) Resmetirom 80 mg (n = 321)	LS Mean %CFB (SE) Resmetirom 100 mg (n = 323)	LS Mean %CFB (SE) Placebo (n = 321)	LS Mean %CFB Difference Resmetirom 80 mg from PBO (95% CI)	LS Mean %CFB Difference Resmetirom 100 mg from PBO (95% CI)
LDL-C Week 24*	-13.6 (1.7)	-16.3 (1.7)	0.11 (1.7)	-13.7 (-17.5, -10.0)	-16.4 (-20.1, -12.6)
p value				<0.001	<0.001
Apo B Week 24	-16.8 (1.3)	-19.8 (1.3)	0.39 (1.3)	-17.2 (-20.0, -14.4)	-20.2 (-22.9, -17.4)
Triglycerides Week 24	-22.7 (4.0)	-21.7 (4.3)	-2.6 (4.1)	-20.1 (-28.3, -11.8)	-19.1 (-27.8, -10.3)
Lp(a) Week 24	-30.4 (3.8)	-35.9 (4.0)	-0.84 (3.5)	-29.5 (-37.6, -21.5)	-35.1 (-43.5, -26.6)
MRI-PDFF Week 52	-35.4 (2.8)	-46.6 (2.8)	-8.7 (2.7)	-26.7 (-32.9, -20.6)	-37.9 (-44.2, -31.7)
ALT Week 48	-26.6 (3.7)	-33.2 (3.9)	-6.9 (3.8)	-19.7 (-27.7, -11.6)	-26.3 (-34.5, -18.1)
AST Week 48	-22.1 (3.9)	-28.3 (3.9)	-2.9 (3.8)	-19.3 (-27.2, -11.3)	-25.4 (-33.5, -17.4)
GGT Week 48	-25.0 (5.5)	-31.9 (6.3)	3.3 (5.2)	-28.3 (-37.3, -19.3)	-35.2 (-45.5, -25.0)

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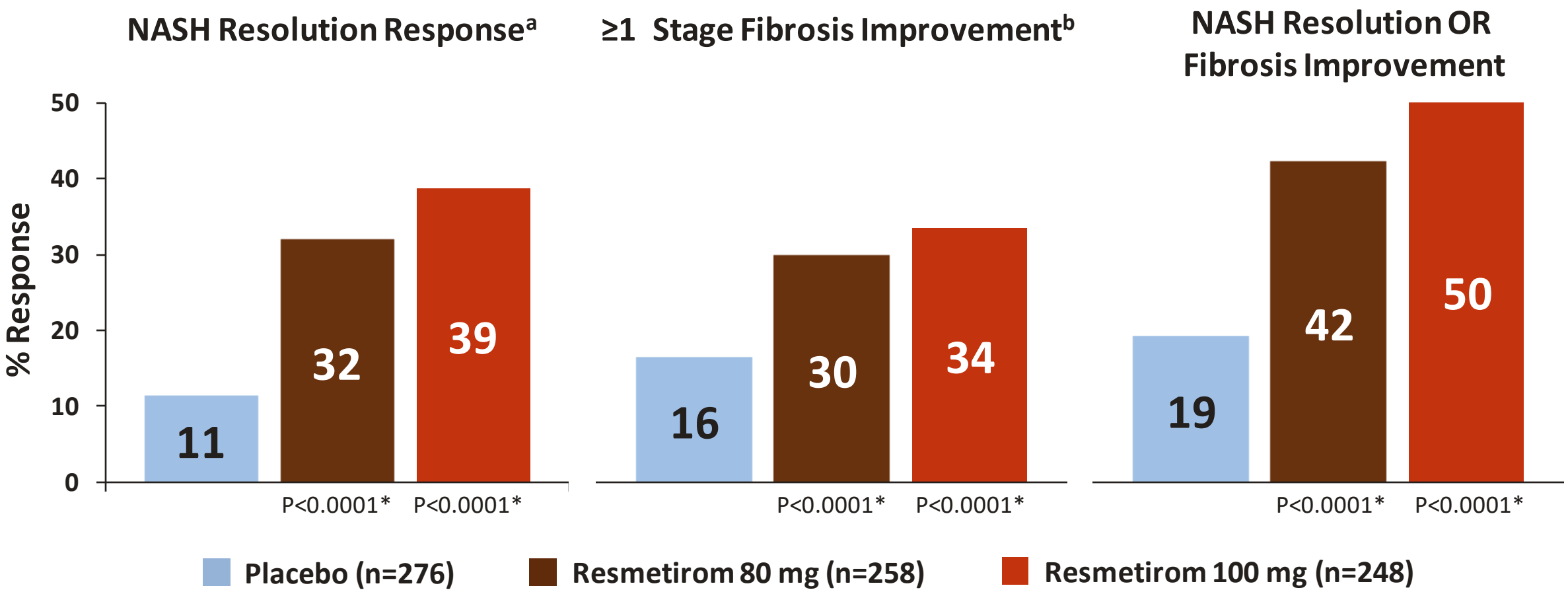
Supportive Analyses of Dual Primary Endpoints

MAESTRO NASH Baseline + Week 52 Liver Biopsy Population



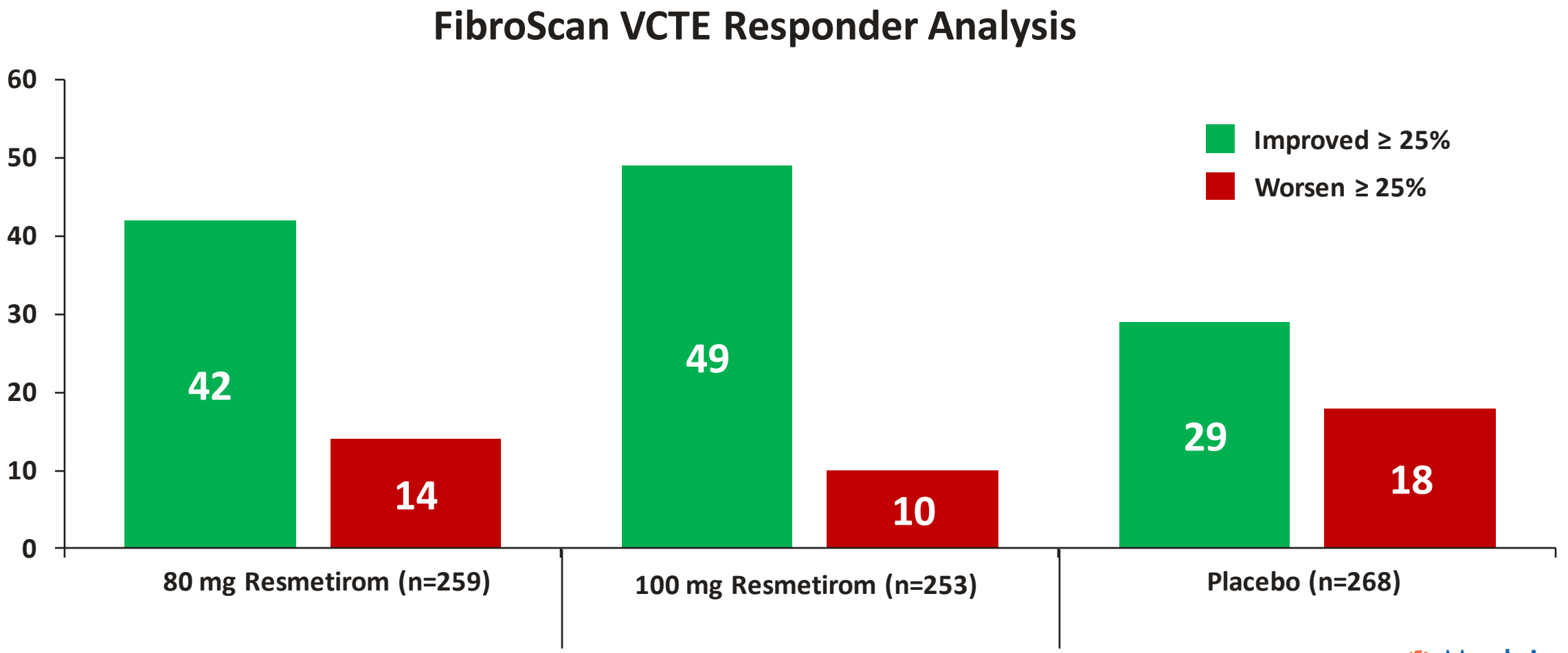
[a] NASH Resolution response: NASH resolution (ballooning 0,1) with at least a 2-point improvement in NAS and no worsening of fibrosis

[b] Fibrosis improvement response: ≥1 stage improvement in fibrosis with no worsening of NAS

* All P values are nominal.

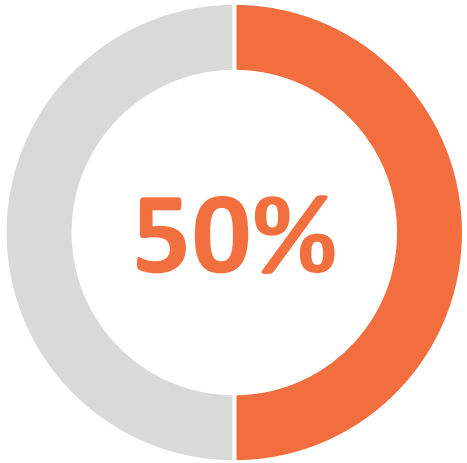
Change from Baseline in FibroScan VCTE/LSM by Fibrosis Stage (NEJM)

MAESTRO NASH Week 52 Primary Analysis Population

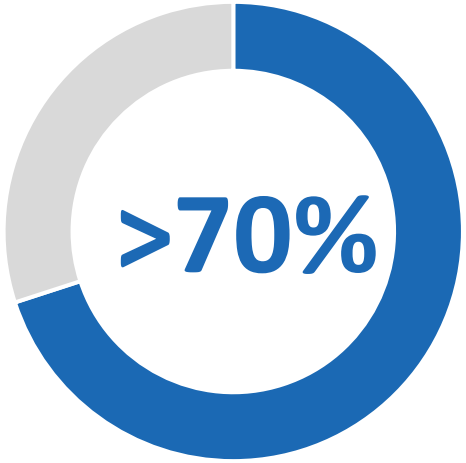


LSM, liver stiffness measurement; PBO, placebo; VCTE, vibration-controlled transient elastography.

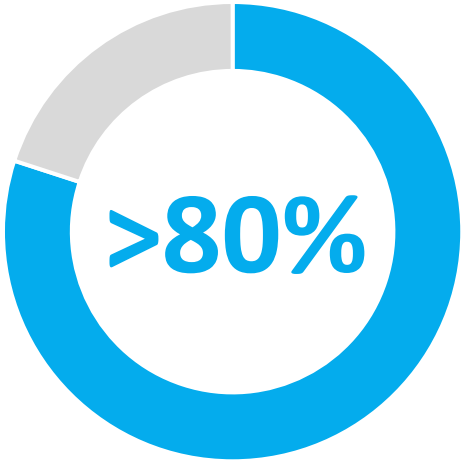
Phase 3 Data in *New England Journal of Medicine* Demonstrate Broad Response



50% of Rezdiffra-treated patients showed either **NASH resolution or fibrosis improvement**[1]



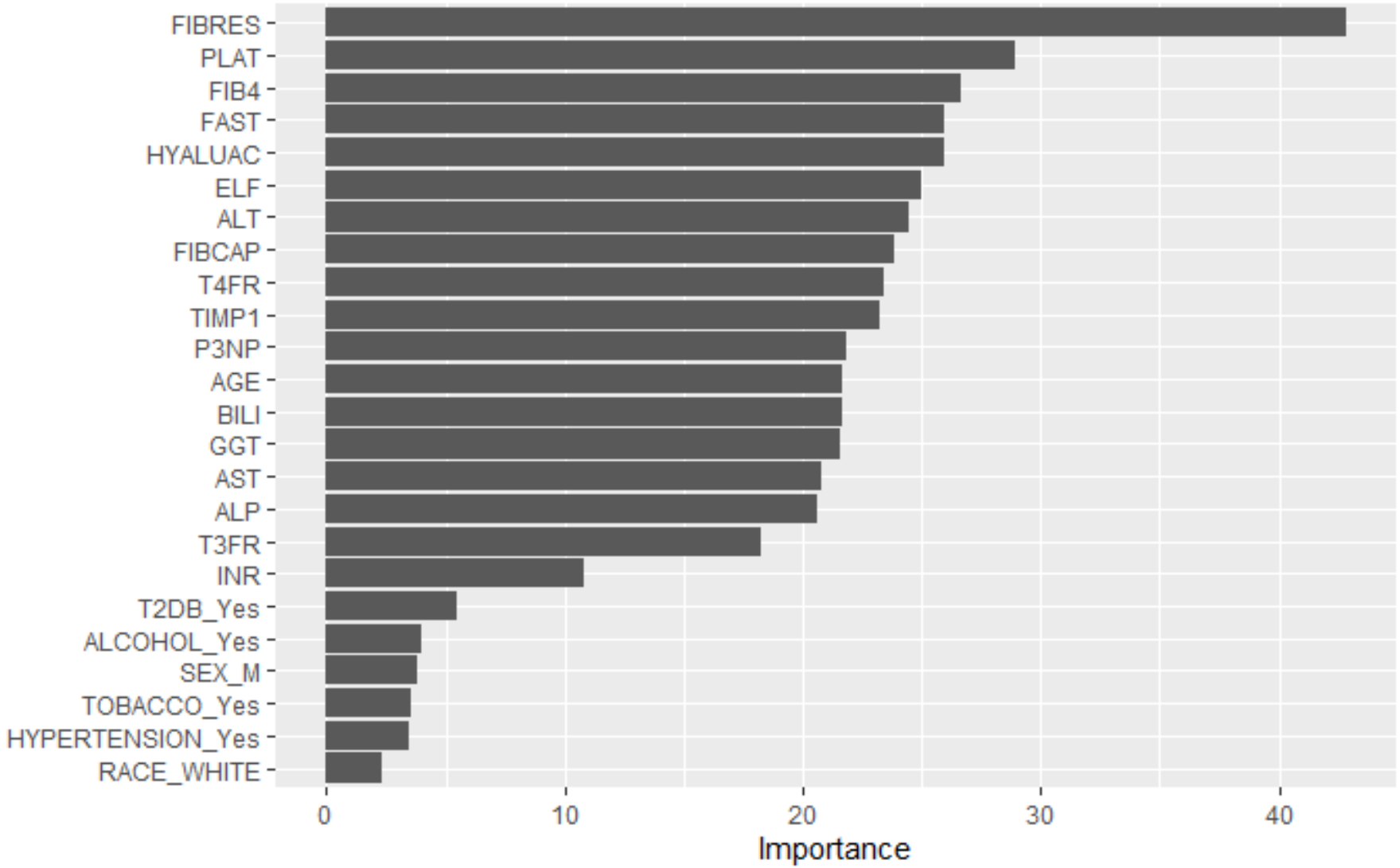
>70% of patients achieved a **>30% reduction in non-invasive test results (MRI-PDFF)**[2]



> 80% of Rezdiffra-treated patients achieved **fibrosis reversal or no fibrosis progression**[3]

MRI-PDFF, magnetic resonance imaging-proton density fat fraction. Source: Harrison S, et al. *N Engl J Med*. 2024 Feb;390(6):497-509. 1. 50% of patients on 100mg with eligible biopsies at 52 weeks achieved NASH resolution or fibrosis improvement. *NEJM* supplement Table S9. 2. >70% of patients on 100mg achieved >30% reduction in MRI-PDFF at 52 weeks. *NEJM* supplement Table S10. 3. >80% of Rezdiffra-treated patients (F1B or F2 at baseline) achieved fibrosis reversal or no fibrosis progression at 52 weeks. *NEJM* supplement Figure S5.

Lean Predictor Model V2 For Baseline Fibrosis (Based on Biopsy)



Random Forest – Variable Importance Plot

Biomarkers were evaluated for their ability to predict baseline fibrosis on biopsy

A lean set of generally available biomarkers were studied

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AUC performance of RF Models in Cross Validation

Full Predictor Model vs. Lean Predictor Model V1 vs. Lean Predictor Model V2

3-class prediction:

Model	0/1A/1C vs Rest Mean (SD)	1B/2/3 vs Rest Mean (SD)	4 vs Rest Mean (SD)
Full Predictor Model	0.804 (0.055)	0.776 (0.047)	0.930 (0.031)
Lean Predictor Model V1	0.854 (0.017)	0.815 (0.018)	0.890 (0.028)
Lean Predictor Model V2	0.755 (0.033)	0.696 (0.030)	0.896 (0.026)

Model	# Patients	# Predictors
Full Predictor Model	607	36
Lean Predictor Model V1	1765	21
Lean Predictor Model V2	1247	24

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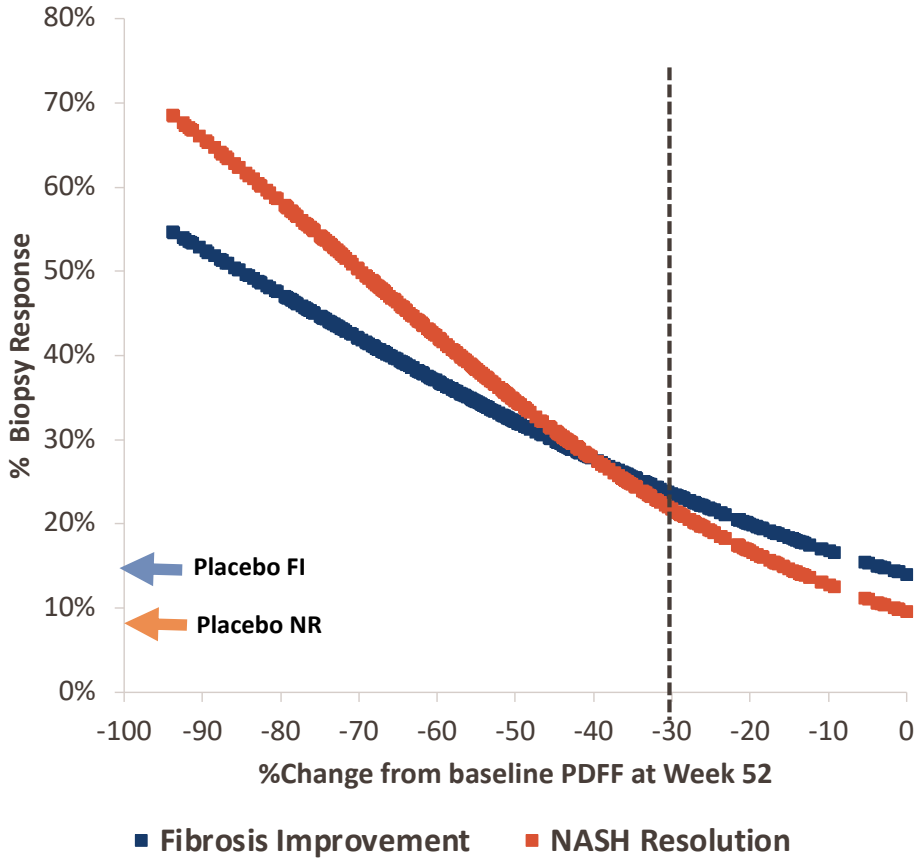
Ongoing Efforts to Define Response Noninvasively



- PDFF reduction in resmetirom treated patients was highly associated with both NASH Resolution (NR) and Fibrosis Improvement (FI)
  - Placebo patients with more PDFF reduction had more NASH reduction but not fibrosis improvment
- At least a 30% PDFF response was observed in 96%, 88%, and 92% of resmetirom 100 mg responders for NASH resolution, Fibrosis improvement, and NASH resolution or Fibrosis improvement

All resmetirom treated patients (80 mg and 100 mg combined)

Logistic regression model, predicting response on biopsy as a function of % change from baseline in MRI-PDFF

MASH versus NASH

- No inclusion of term MASH
  - Metabolic dysfunction associated steatohepatitis, including at least one metabolic risk factor, (obesity/diabetes/dyslipidemic or on statins/hypertension)
- FDA- Use of MASH is premature
- ICD 10 coding not yet in place: many societies have accepted use of the term MASH
- EMA required use of MASH- proposed indication is MASH/NASH

Analyses of Liver Enzymes are Not According to Protocol or NASH Guidelines

Table 2 presents the frequency of liver test elevations during Trial 1.

Table 2: Frequency of Liver Test Elevations in Trial 1

	Placebo (%)	REZDIFFRA 80 mg Once Daily (%)	REZDIFFRA 100 mg Once Daily (%)
ALT > 3x ULN	10	11	13
ALT > 5x ULN	2	2	2
AST > 3x ULN	10	9	12
AST > 5x ULN	2	1	4
TBa > 2x ULN	2	1	3

TB elevations include patients with Gilbert syndrome.

Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis

Arie Regev[1] | Melissa Palmer[2] | Mark I. Avigan[3] | Lara Dimick-Santos[3] | William R. Treem[4] | John F. Marcinak[5] | Daniel Seekins[6] | Gopal Krishna[7] | Frank A. Anania[3] | James W. Freston[8] | James H. Lewis[9] | Arun J. Sanyal[10] | Naga Chalasani[1]

- The liver enzyme section of adverse events with description of resmetirom and placebo patients
  - Does not take into consideration this population (NASH) with elevated baseline liver enzymes and high degree of fluctuations in liver enzymes ; this section does not adhere to the protocol definitions or consensus on evaluation of liver enzymes in patients with NASH
  - Confusing to prescribers

Thanks

- The Madrigal team
- The Patients
- The Investigators and sites
- The thought leaders who paved the way