Resmetirom

A Thyroid hormone Receptor-β Agonist for the Treatment of NASH PHASE 3 Results

Becky Taub

CMO and President R&D

Madrigal Pharmaceuticals

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MAESTRO-NASH

Study Design: Randomized, Double-Blind, Placebo Controlled

Inclusion/Exclusion

- ≥3 metabolic risk factors (Metabolic Syndrome)
- FibroScan **kPa consistent with F2-3**
- FibroScan **CAP ≥280**
- **≥8% liver fat** on MRI-PDFF
- **NAS≥4** with fibrosis stage 1A/C with elevated PRO-C3 (up to 3%) 1B, total F1 up to 15%; F3, at least 50%, the rest F2

Dual Primary Endpoints – Week 52

- Dual: Resolution of NASH (ballooning 0; inflammation 0,1) with at least 2-point reduction in NAS and no worsening of fibrosis

OR

- Reduction in fibrosis stage by 1-point with no worsening of NAS

Key secondary endpoints LDL-C lowering at Week 24

Composite liver-related outcome at 54 months [histologic evidence of cirrhosis on biopsy, MELD>=15, hepatic decompensation, liver transplant, all cause mortality]

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MAESTRO-NASH-Baseline Characteristics

	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)	Overall (N=966)
Age	56 (12)	57 (11)	57 (11)	57 (11)
Female	182 (57)	182 (56)	178 (56)	542 (56)
White	291 (90)	291 (90)	281 (88)	863 (89)
Hispanic or Latino	71 (22)	81 (25)	52 (16)	204 (21)
BMI	36 (6)	36 (7)	35 (7)	36 (7)
Type 2 Diabetes	224 (70)	213 (66)	210 (65)	647 (67)
Hypertension	243 (76)	254 (79)	257 (80)	754 (78)
Dyslipidemia	230 (71)	236 (73)	223 (70)	689 (71)
Hypothyroid	38 (12)	46 (14)	45 (14)	129 (13)
FibroScan VCTE	13 (7)	14 (7)	13(6)	13 (7)
FibroScan CAP	346 (37)	349 (39)	347 (37)	348 (38)
MRI-PDFF	18 (7)	17 (7)	18 (7)	18 (7)
Baseline Liver Biopsy				
NAS >= 5	266 (83)	288 (89)	253 (79)	807 (84)
Fibrosis 1B	16 (5)	15 (5)	18 (6)	49 (5)
Fibrosis 2	107 (33)	100 (31)	112 (35)	319 (33)
Fibrosis 3	199 (62)	208 (64)	191 (60)	598 (62)

Data are mean (SD) or n (%)

MAESTRO-NASH: Liver Biopsy (ITT) at Week 52

- Central read of all eligibility
- 966 ITT of primary population includes all patients with at least a baseline biopsy with appropriate fibrosis stage; 955 mITT due to COVID biopsy site closure delaying 11 Week 52 biopsies to >60 weeks
- Biopsies rescored as F1A, C were considered exploratory and will be evaluated separately
- All baseline and Week 52 biopsies were read independently by two central pathologists (on glass slides) for the primary analysis read, read in large groups of baseline (spiked with screen fail biopsies) or Week 52
  - All biopsies were read as digitized images in a secondary analysis and to provide a comparison between each pathologist's read on glass and digitized image
  - Each pathologist's scores calculated by the data team showed a similar statistically significant magnitude of response at both doses for both primary liver biopsy endpoints
  - The results were combined statistically to generate a single treatment effect
- All biopsies were read by two AI platforms, one PATHAI read digitized images

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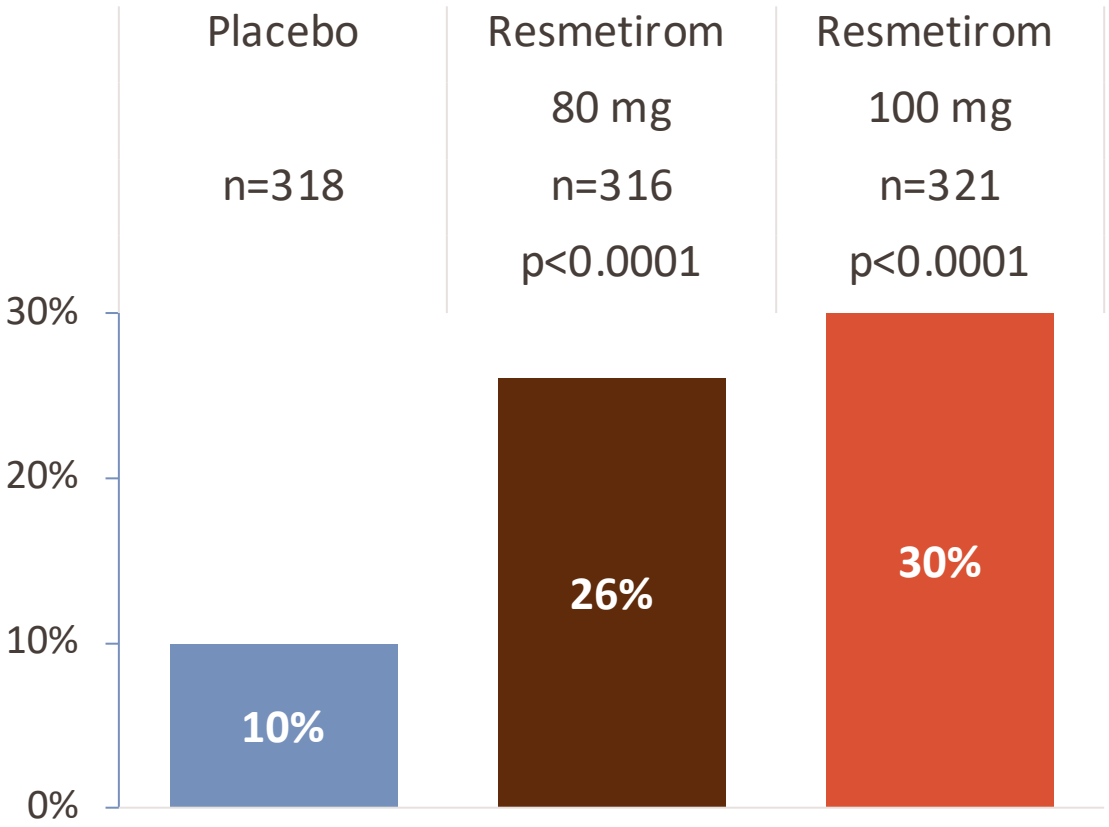
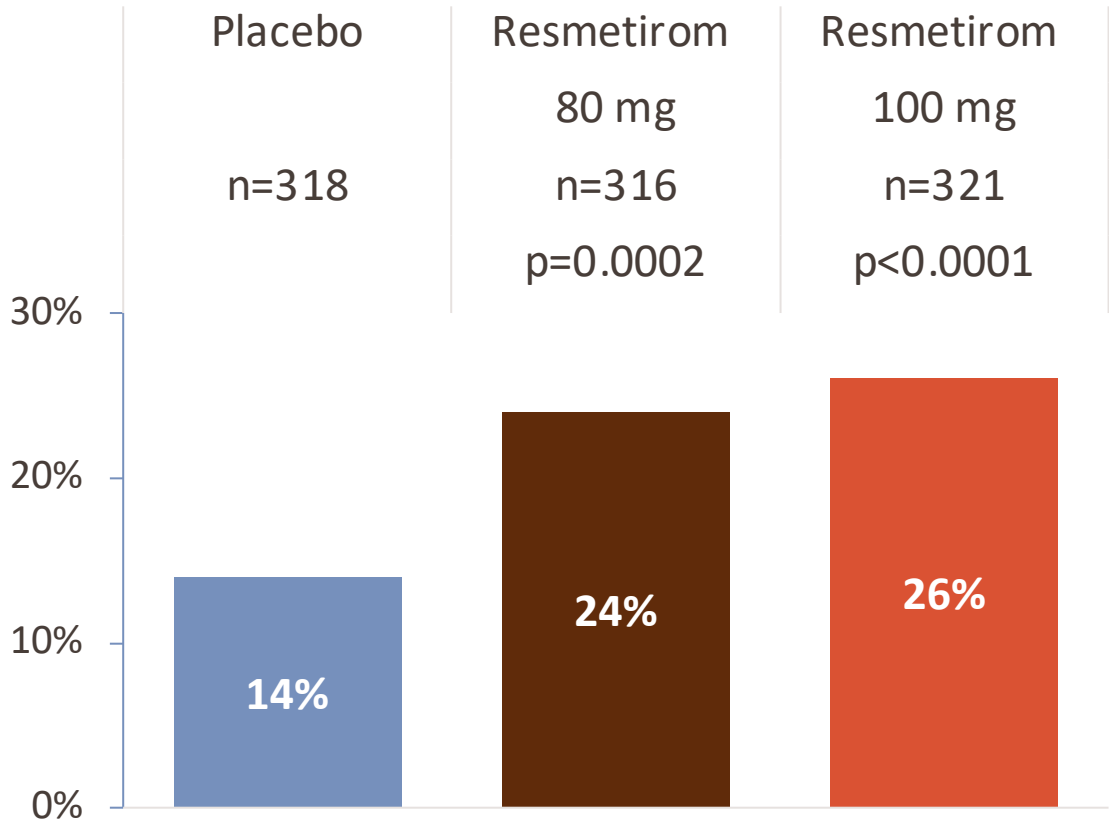
MAESTRO-NASH

NASH Resolution



Fibrosis Improvement (≥ 1 stage)



Primary Endpoints After Consensus Assessment

Primary Endpoint	Resmetirom 80 mg (n=316)	p-value	Resmetirom 100 mg (n=321)	p-value	Placebo (n=318)
NASH resolution (ballooning 0, inflammation 0,1) with ≥2-point reduction in NAS and no worsening of fibrosis	24%	<0.0001	28%	<0.0001	8%
≥1-stage improvement in fibrosis with no worsening of NAS	24%	<0.0001	26%	<0.0001	12%

- As a supportive analysis, a consensus read of digitized images was conducted in cases where the two pathologists scores disagreed as to whether the there was a response for either NASH Resolution (ballooning 0,1; 2-pt NAS reduction and no worsening of fibrosis) OR >=1 stage Fibrosis reduction with no worsening of NAS (primary endpoints)
- Pathologists jointly read component(s) from a digitized image(s) from the case that would resolve the difference
  - Typically (~90%) differences were minor and related to a single component score
- The results of the consensus analyses fully confirmed the primary results obtained using statistical methodology

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Worsening of NASH

- NAS NAFLD Activity Score was developed to define NASH for the purpose of use in clinical trials
- Score (NAS), which specifically includes only features of active injury that are potentially reversible in the short term. The score is defined as the unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2); thus ranging from 0 to 8.

- DRAFT FDA Guidance
  - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) **and** No worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis)
- No worsening of NASH Equals:
  - No increase in NAS, the sum of the scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2); thus ranging from 0 to 8 for ballooning, inflammation, or steatosis

- Meaning that an increase in any of the 3 components that leads to an increase in NAS is ”worsening of NASH”

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An increase in any of the 3 components independent of effect on NAS

		Ballooning	Lobular Inflammation	Steatosis	NAS	Fibrosis
Example 1	Baseline	2	1	2	5	3
	End of Rx	0	**2**	1	3	2
Example 2	Baseline	2	2	1	5	3
	End of Rx	0	1	**2**	3	2

- Example 1
  - Baseline, fulfills definition of NASH NAS>=4 with all components, F3;End of treatment, Fibrosis decreased by 1, NAS <4, and no ballooning, this is indeterminant or not NASH
- Example 2
  - Baseline fulfills criteria for NASH; end of Rx NASH is resolved, fibrosis is improved, this is NASH Resolution not “worsening” of NASH (increase of steatosis by 1)
- The “endpoint” in which any component worsening is worsening of “NASH” would say these are not a fibrosis responders because example 1, inflammation increased by 1, even though NAS decreased and the other two components improved; example 2, this is actually NASH resolution, NAS decreased, ballooning 0, inflammation 1 and a reduction in fibrosis
- Pathologist view; increase in NAS or the “Activity” component of SAF should be included in evaluation of the fibrosis endpoint
  - Calling NASH worse based on an increase in a single component when other component(s) decrease and NAS or “Activity” decreases or is unchanged is a “laughable idea” given the variability in scoring any individual component

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THANK YOU

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