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One-year results of the Global Phase 2b randomized placebo-controlled ARREST Trial of Aramchol, a Stearoyl CoA Desaturase modulator in NASH patients

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Galmed Pharmaceuticals

AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Disclosures

V Ratziu: Allergan, Astra-Zeneca, Boehringer-Ingelheim, Enanta, Galmed, Genfit, Intercept, Medimmune, Novartis, Pfizer

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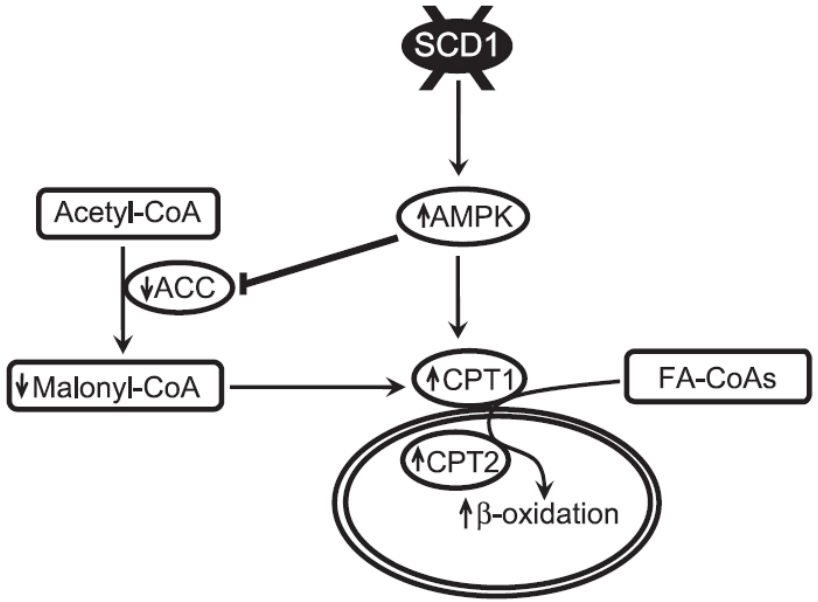
SCD1, a major target for metabolic protection in NAFLD dietary models

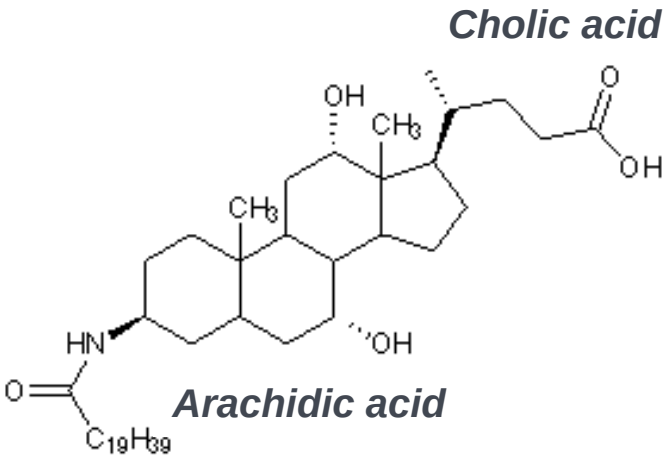
- **Steroyl-CoA desaturase-1 (SCD1) is a key enzyme in hepatic lipogenesis that converts saturated fatty acids into monounsaturated fatty acids**
- **In high fat or high carb dietary models, down regulation of SCD 1 results in [1] :**
  - Resistance to obesity, decreased adiposity
  - Reduced hepatic lipogenesis
  - Enhanced insulin sensitivity
  - Protection from steatosis, hypertriglyceridemia
  - Enhanced lipid oxidation [2]



1. Miyazaki, Cell Metab 2007;6:484-96. Sampath, J Biol Chem 2007;282:2483-93. Cohen, Science 2002;297:240-3

2. Dobrzyn, PNAS, 2004;101:6409-14. Ntambi, PNAS 2002;99:11482-6

Aramchol – Liver targeted SCD1 modulator

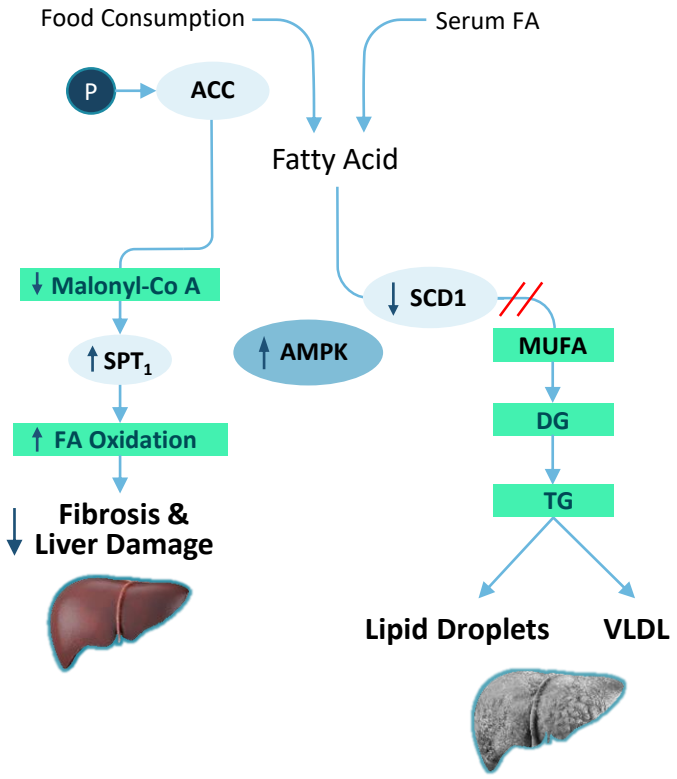


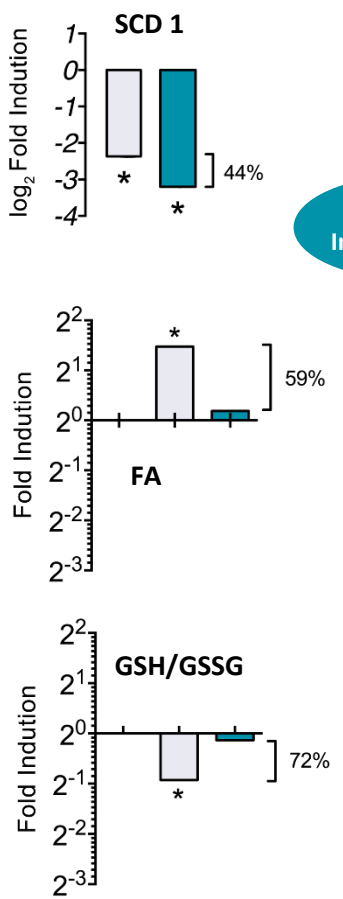
- **FABAC- Fatty acid Bile acid conjugate**
- **Aramchol in pre clinical models:**
  - Inhibition of SCD1 activity in liver microsomes and in HFD NAFLD rodent and dog models
  - Down regulation of liver FA in multiple dietary models [1]
  - Down regulation of collagen in TAA animal models for liver fibrosis [2]
  - Target directly HSC to down regulate collagen and α SMA production *(Friedman S et al. Poster 0738 AASLD 2018)*
- **Aramchol in Phase 2a showed significant reduction in liver fat**

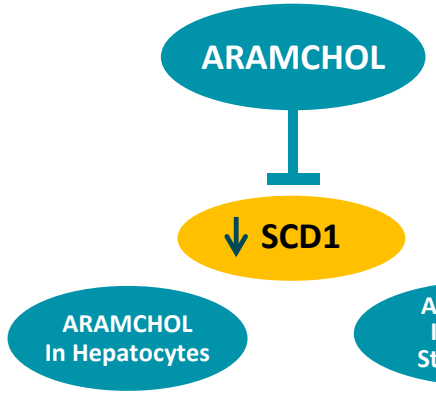
1. Iruarrizaga-Lejarreta, JM Mato, et al. "Role of Aramchol in steatohepatitis and fibrosis in mice. "Hepatology Communications 1.9 (2017): 911-927.
2. R. Golan-Gerstl, S. Reif et al. "The anti-fibrotic effect of Aramchol on liver fibrosis in TAA animal model" EASL 2017 poster
3. Safadi et al. "The fatty acid–bile acid conjugate Aramchol reduces liver fat content in patients with nonalcoholic fatty liver disease." Clinical Gastroenterology and Hepatology 12.12 (2014)

Scientific Rationale for SCD1 Down Regulation in NASH

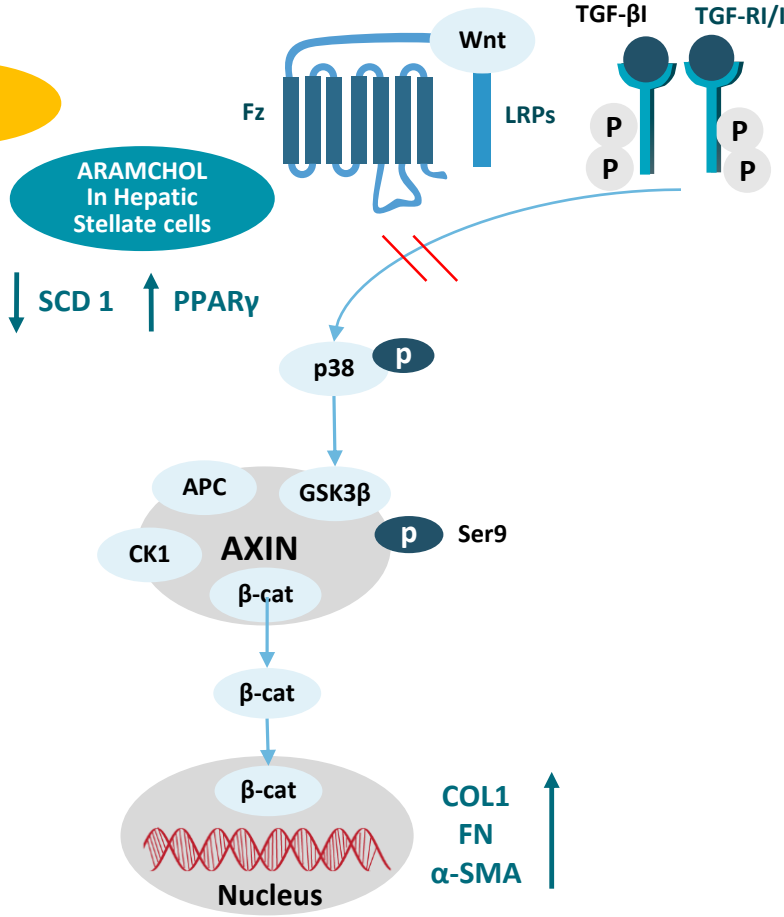
Aramchol in Hepatocytes

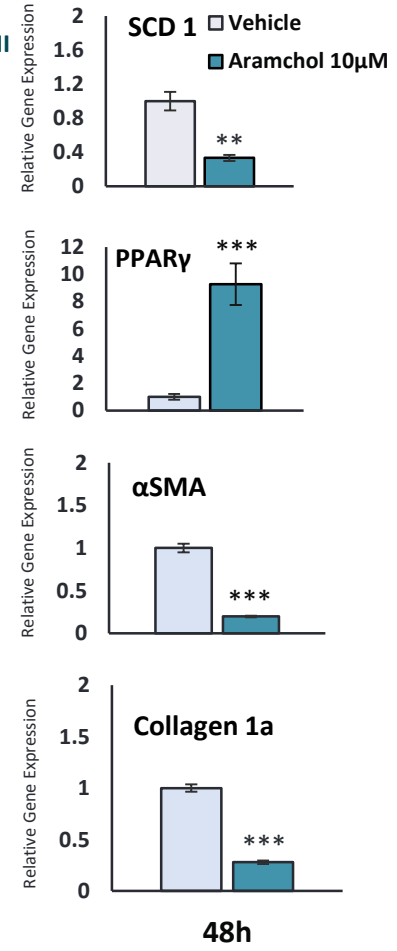




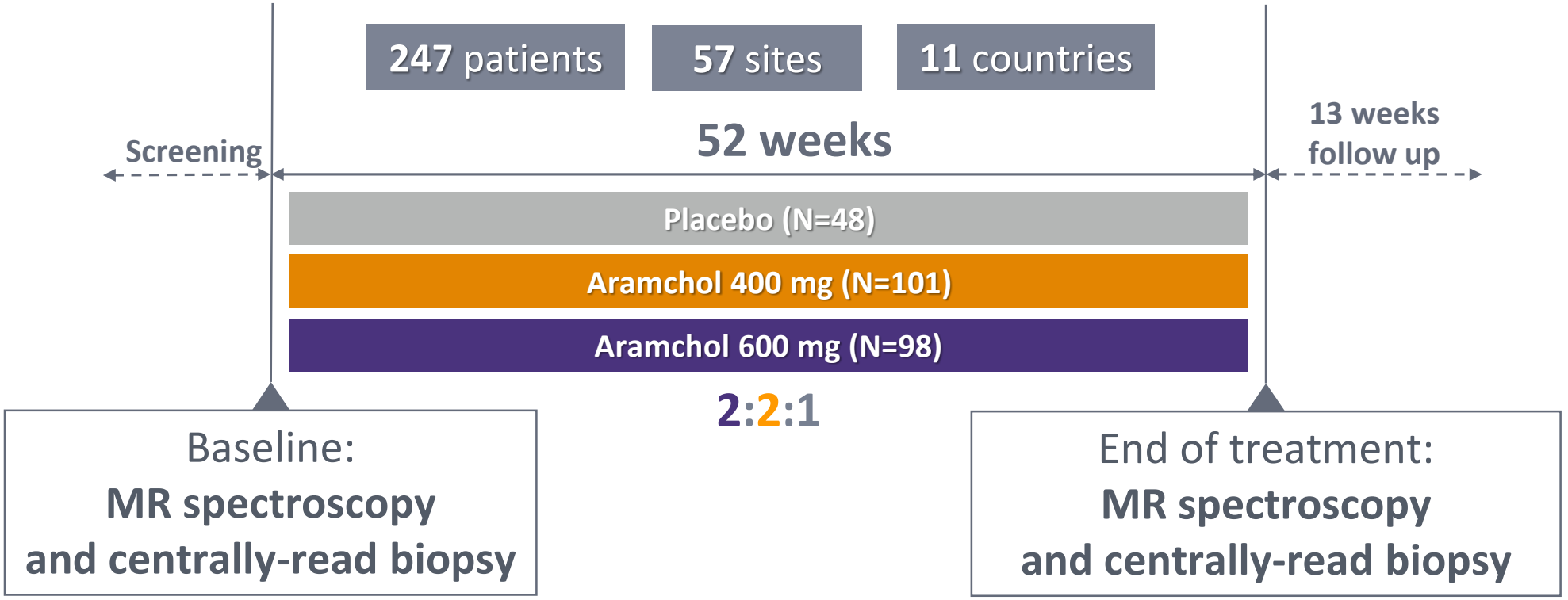


Aramchol in HSC





ARREST: A one year global phase 2b randomized placebo-controlled trial



Key inclusion criteria

- **BMI: 25kg/m² - 40kg/m²**
- **Known type II Diabetes Mellitus or Pre-diabetes**
- **Histologically proven steatohepatitis with NAS ≥4:**
  - Central reading performed by Prof. Carolin Lackner at the University of Graz Austria
- **Liver fat concentration of 5.5% or more as measured by MRS**
  - Central reading performed by Prof. Dafna Ben Bashat at the Sourasky Medical Center, Israel
- **Normal synthetic liver function**

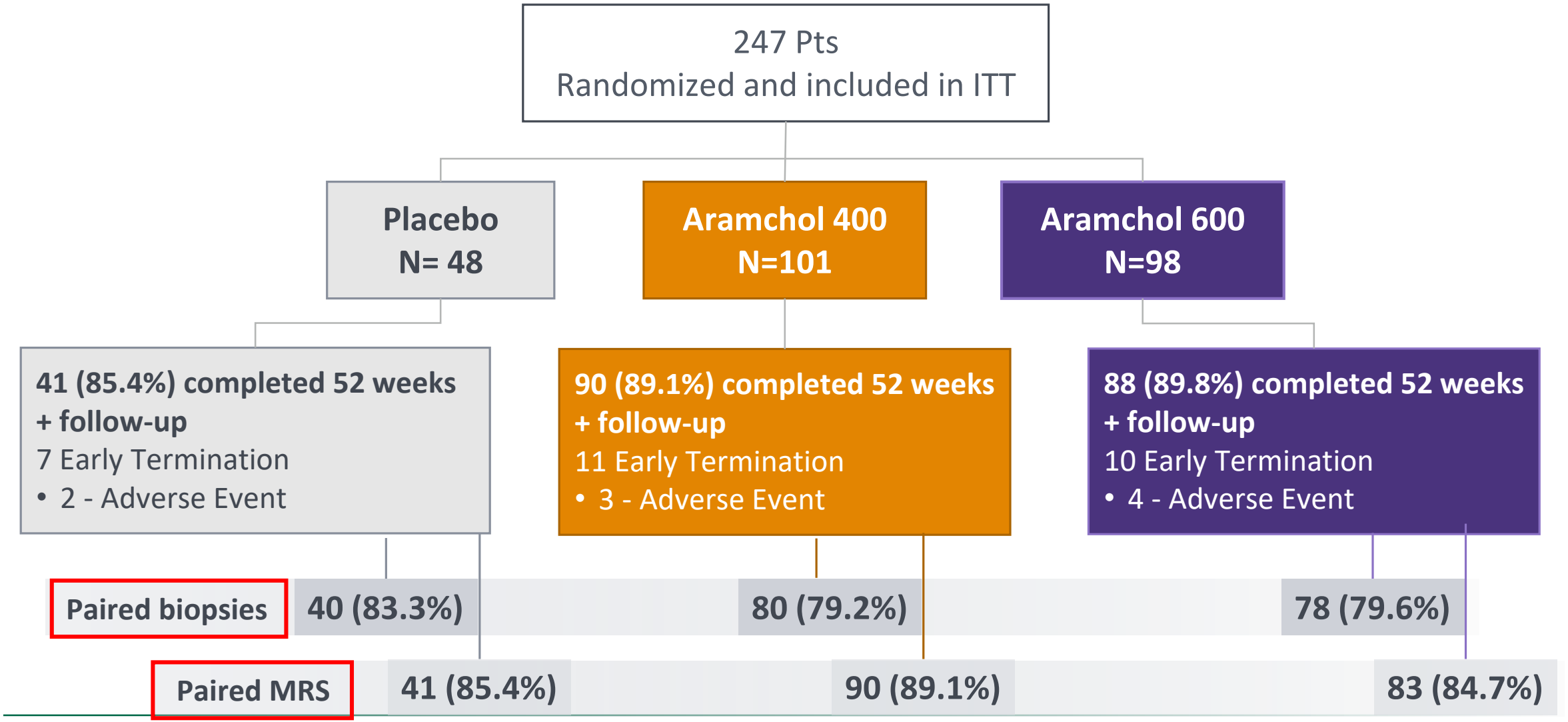
Key exclusion criteria

- **Cirrhosis**
- **Patients with other active (acute or chronic) liver disease**
- **Weight loss of more than 5% within 6 months**
- **Bariatric surgery within 5 years**
- **HIV**
- **Diabetes mellitus other than type II**
- **Treatment with other anti-diabetic medications**
  - Unless started prior to biopsy (6/12 months depending on drug) and stable
- **Uncontrolled arterial hypertension**
- **Uncontrolled hypothyroidism**
- **Renal dysfunction eGFR< 40 ml/min**

Endpoints

- **Primary endpoint: Absolute % change from baseline to end of study in liver fat content measured by MR Spectroscopy**
  - Matched regions of interest
  - Mixed model repeated measures
  - **Covariates:** Treatment group, country, age, sex, baseline MRI and baseline BMI
- **Key secondary endpoints:**
  - Fibrosis score improvement (≥ 1 stage) without worsening of NASH (increase of inflammation and or ballooning)
  - NASH resolution (ballooning 0 and inflammation 0-1) without worsening of fibrosis
  - Biopsy analyses: Baseline adjusted logistic regression stratified by country with the following effects: treatment group, baseline fibrosis and NAS
  - Change from baseline in ALT and AST

Disposition

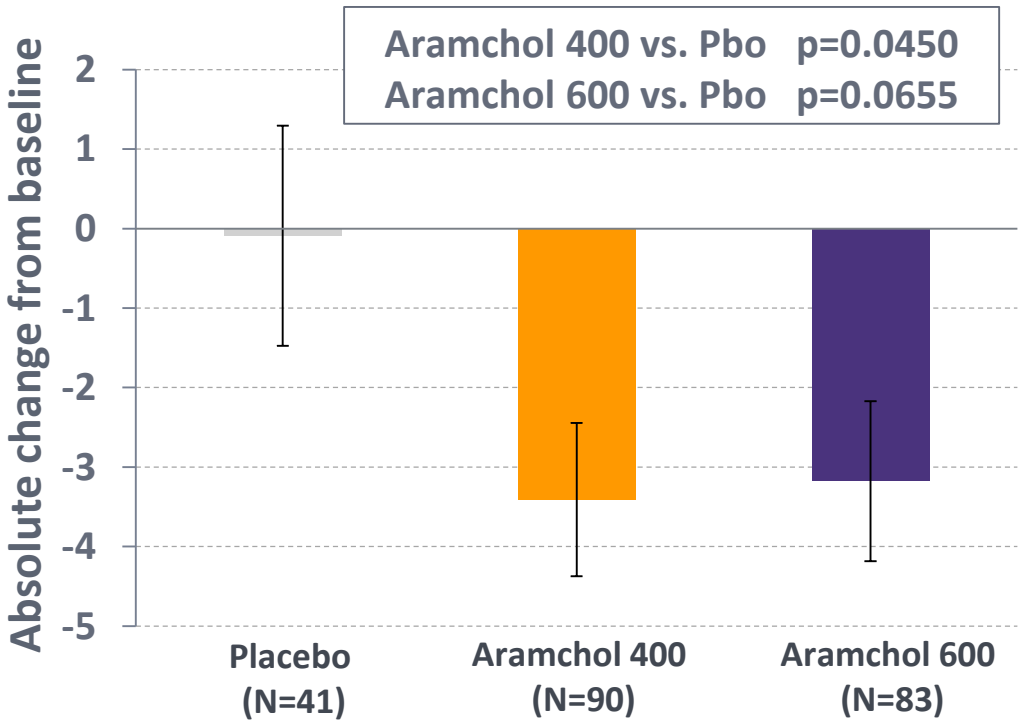


Baseline characteristics

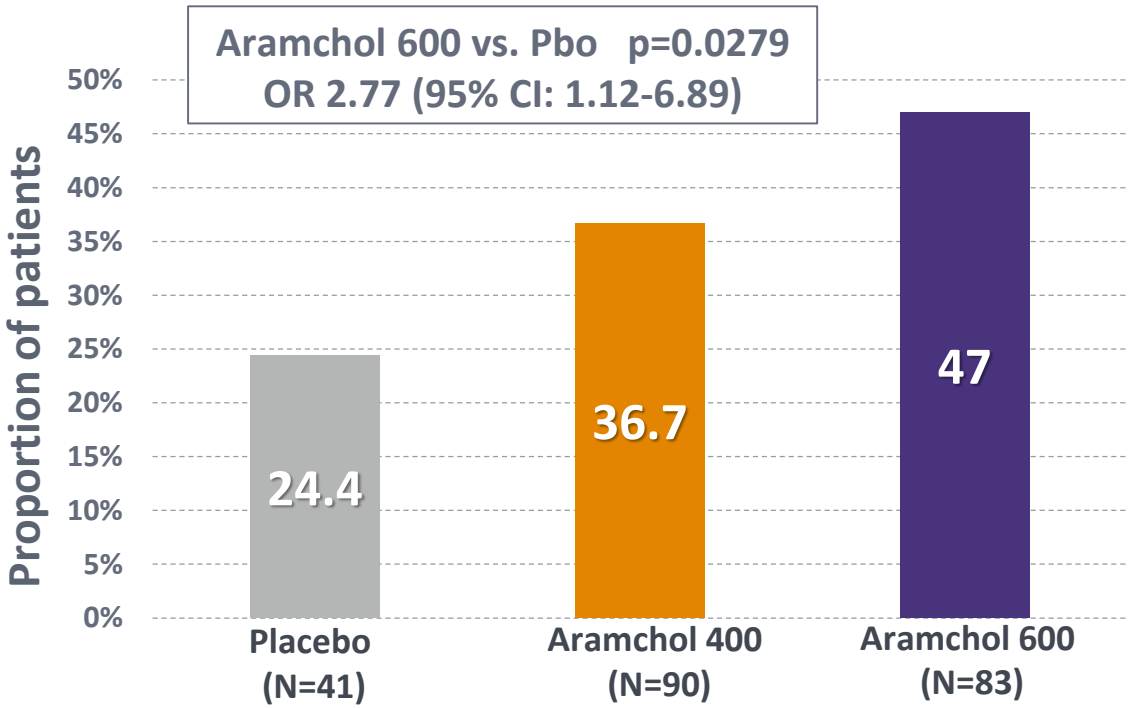
	Placebo	400 mg	600 mg	ALL
Age years, mean (SD)	54.4 ± 10.3	53.9 ± 10.9	54.9 ± 9.8	54.4 ± 10.3
Female sex	52.1%	64.4%	71.4%	64.8%
White	62.5%	62.4%	64.3%	63.2%
Hispanic/Latin/Latin American	33.3%	33.7%	29.6%	32%
Weight kg, mean (SD)	88.6 ± 18.2	88.1 ± 17.4	86.9 ± 15.5	87.7 ± 16.8
BMI kg/m2, mean (SD)	32.6 ± 4.9	32.4 ± 4.5	33 ± 4.2	32.7 ± 4.4
Hemoglobin A1c %	6.5 ± 1	6.5 ± 0.9	6.7 ± 1.0	6.6 ± 1
Hypertension	50%	52.5%	59.2%	54.7%
Dyslipidemia	62.5%	63.4%	48%	57.1%
ALT U/L, mean (SD)	67.7 ± 47.5	68.1 ± 48.3	55.9 ± 37.8	63.1 ± 44.4
Liver Fat-MRS %, mean (SD)	27.5% ± 9.3	27.3% ± 11.8	30.2% ± 12.4	28.5% ± 11.7
NAS score, mean (SD)	5.06 ± 1.26	5.06 ± 0.94	5.21 ± 0.93	5.12 ± 1.00
Fibrosis stage, mean (SD)	1.77 ± 0.99	2.16 ± 0.92	1.96 ± 0.95	2.00 ± 0.96
Fibrosis stage 2/3	16.7% F2	18.8% F2	22.4% F2	60% F2/3
	33.3% F3	47.5% F3	36.7% F3	

Results: Primary endpoint – Absolute Reduction in Liver Fat

Mean absolute change from baseline in liver fat



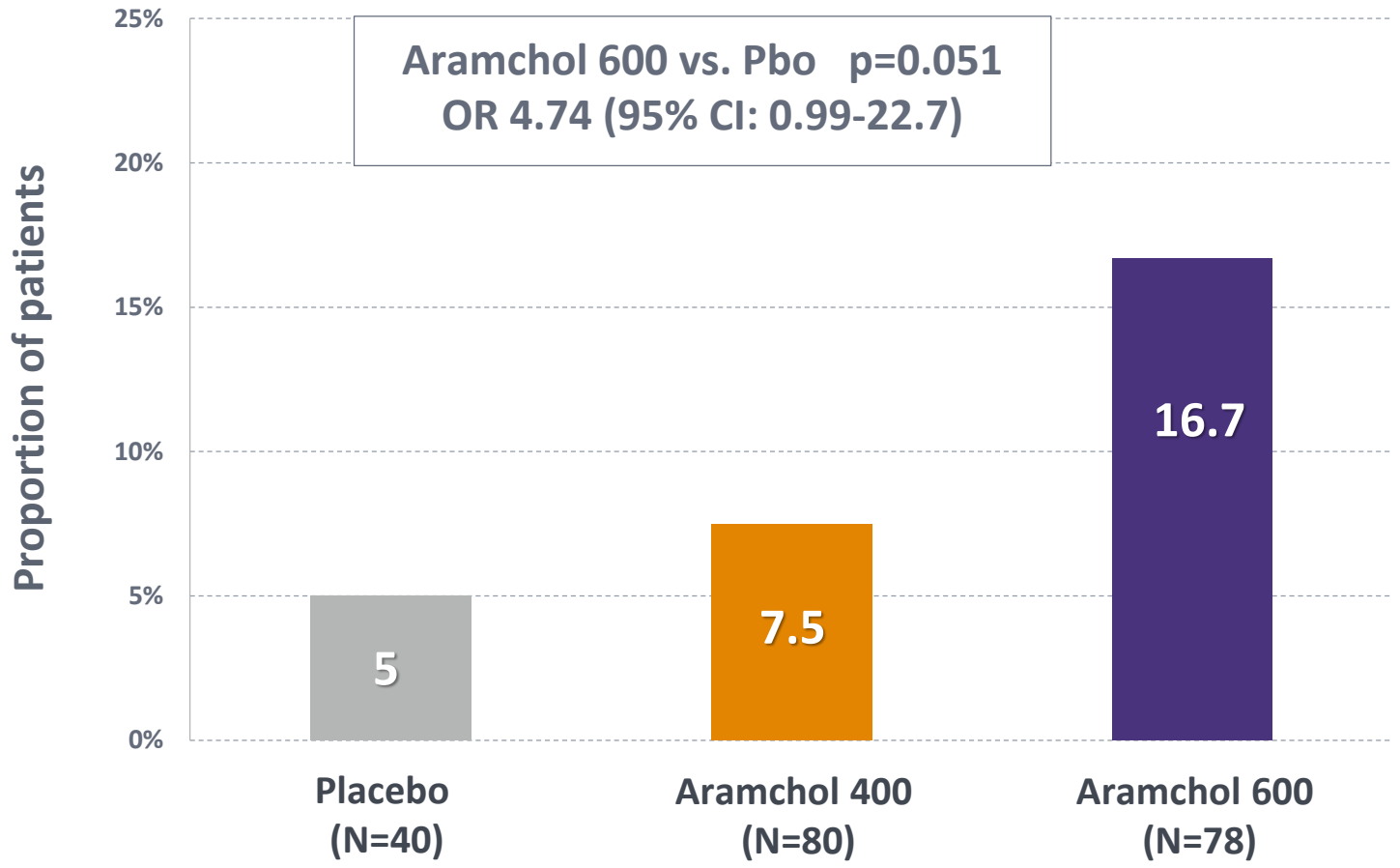
≥5% ABSOLUTE reduction from baseline



≥30% RELATIVE reduction from baseline

Placebo	Aramchol 400	Aramchol 600
14.6 %	25.6 %	30.1%

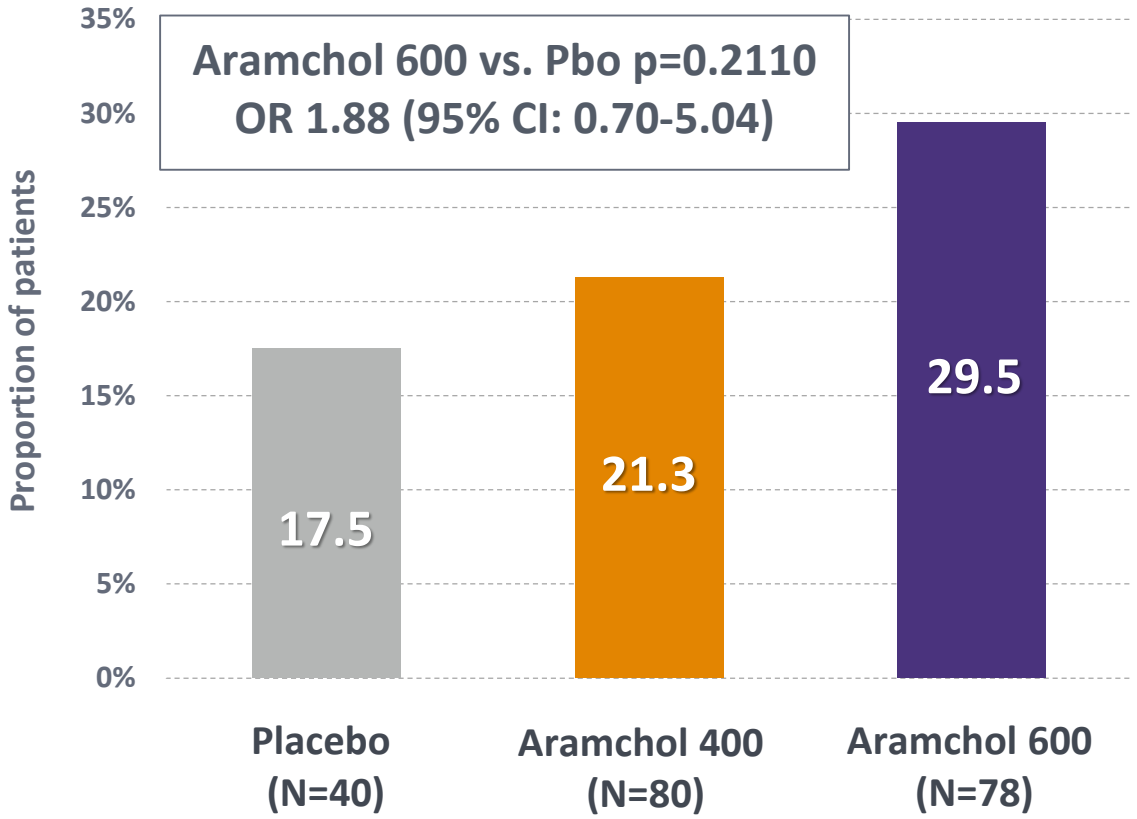
Results: NASH resolution without worsening of fibrosis



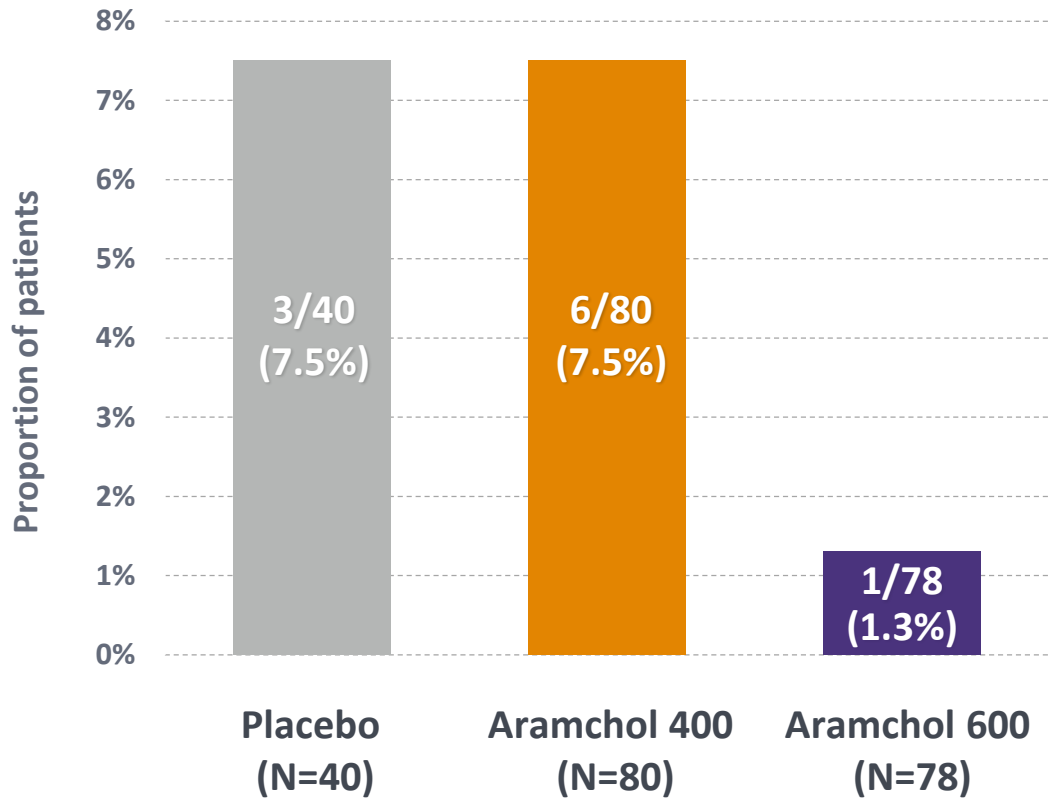
NASH RESOLUTION ALONE :	**7.5 %**	**12.5 %**	**19.2 % (p=0.046)**

Results: Fibrosis improvement and progression to cirrhosis

Fibrosis improvement (≥1 stage) without worsening of NASH

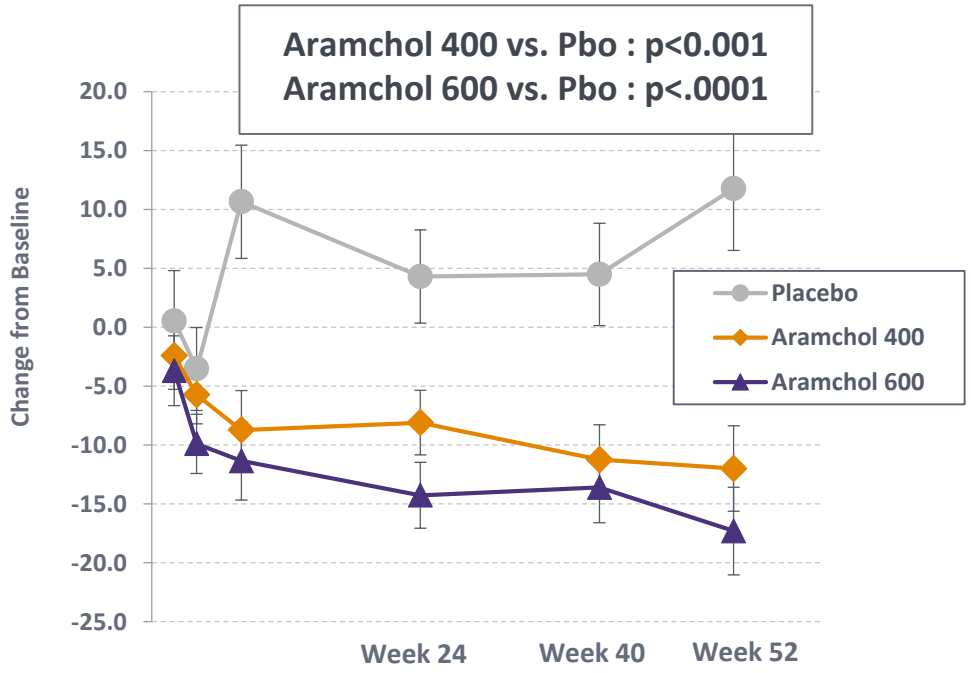


Progression to Cirrhosis



Change from baseline in ALT and AST

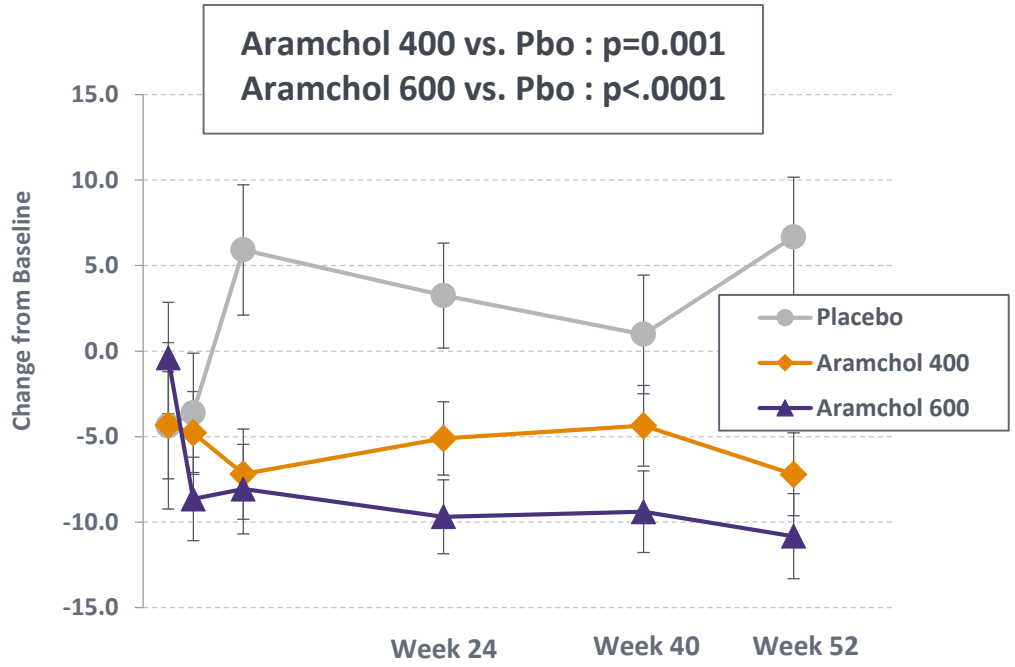
Change from Baseline in ALT (U/L)



ALT normalization, %

Placebo	Aramchol 400 mg	Aramchol 600 mg
13.3	21.9	29

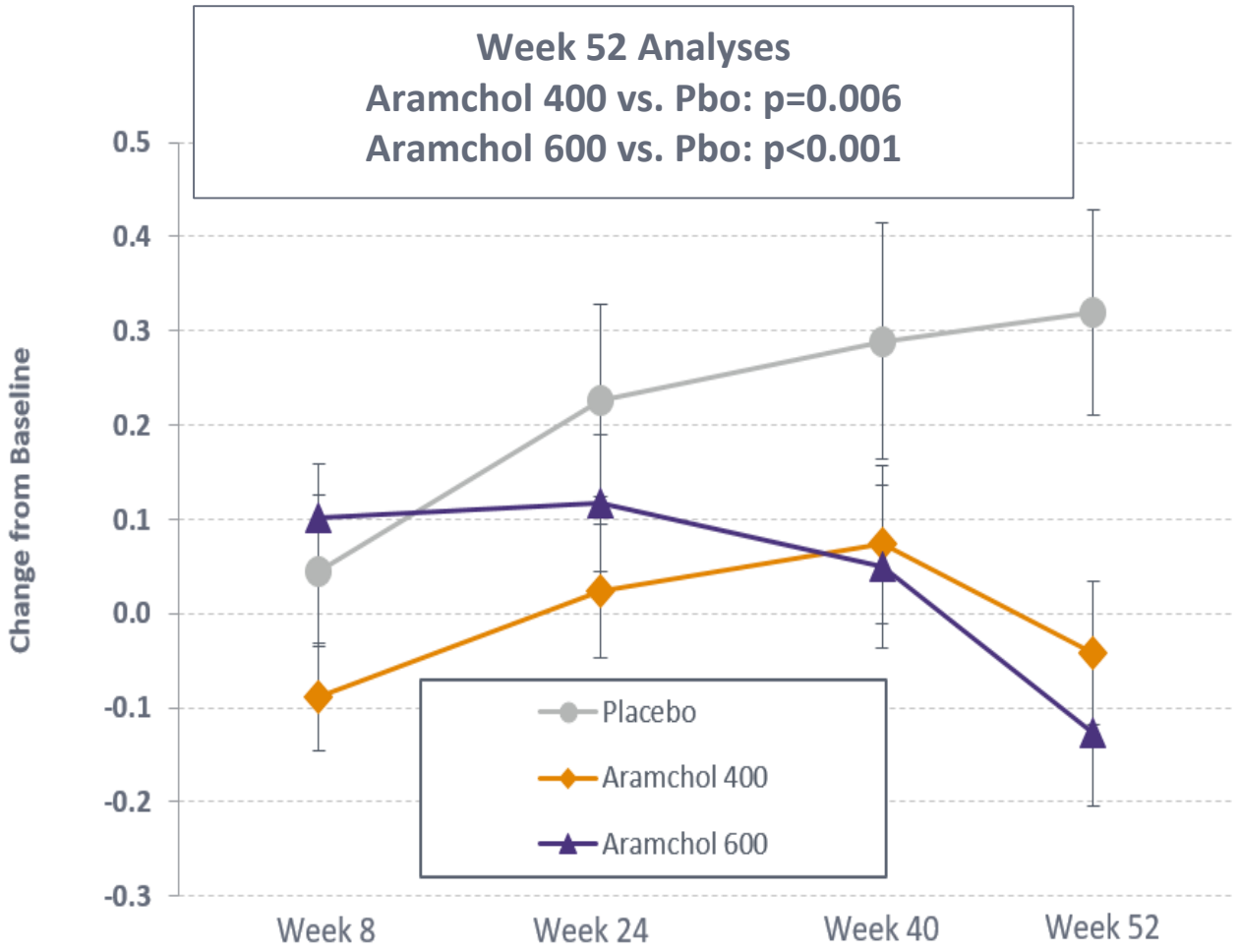
Change from Baseline in AST (U/L)



AST normalization, %

Placebo	Aramchol 400 mg	Aramchol 600 mg
4.4	18.8	22.6

Change from baseline in HbA1c



Results: Safety and tolerability

- **Discontinuation due to adverse events was less than 5% :**
  - 4.2%, 3% and 4.1% of patients in placebo, Aramchol 400mg and 600mg arms respectively
- **SAEs reported in 12.5%, 8.9% and 9.2% of patients in placebo, 400mg and 600mg arms respectively; no deaths**
- **No signal for hepatotoxicity**
- **Weight neutral and no changes in lipid parameters**

Most frequent AEs (≥7% of subjects in at least one study arm)

Adverse event N (%)	Placebo (N=48)	400 mg (N=101)	600 mg (N=98)
Constipation	6 (12.5)	5 (5)	8 (8.2)
Cough	4 (8.3)	4 (4)	5 (5.1)
Fatigue	4 (8.3)	8 (7.9)	3 (3.1)
Headache	6 (12.5)	14 (13.9)	15 (15.3)
Influenza	2 (4.2)	8 (7.9)	5 (5.1)
Nausea	6 (12.5)	10 (9.9)	9 (9.2)
Pruritus	3 (6.3)	7 (6.9)	11 (11.2)
UTI	3 (6.3)	15 (14.9)	13 (13.3)

Conclusion

- Aramchol is a novel, first in class SCD1 modulator, targeted to the liver reducing liver fat and collagen production
- In a one year study, Aramchol showed liver fat reduction, biochemical improvement, NASH resolution and fibrosis reduction in a dose response pattern
- In particular, compared to placebo, the Aramchol 600 mg arm had higher rates of :
  - **NASH resolution without worsening of fibrosis**
  - **Fibrosis stage reduction without worsening of NASH**
  - **Decrease in ALT, AST and better glycemic control (HbA1c)**
- Aramchol showed excellent safety and tolerability profiles
- **Results place Aramchol 600mg among advanced therapeutic candidates for NASH and support further testing in a phase 3 trial**

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Efrat Broide	Beer Yaakov

In Memoriam of **Prof. Tuvia Gilat**, MD 1931-2011

Visionary of Aramchol