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

Disclosures

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

Grant support: Gilead, Intercept
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:
  - Resistance to obesity, decreased adiposity
  - Reduced hepatic lipogenesis
  - Enhanced insulin sensitivity
  - Protection from steatosis, hypertriglyceridemia
  - Enhanced lipid oxidation


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
  • Down regulation of collagen in TAA animal models for liver fibrosis
  • 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

Scientific Rationale for SCD1 Down Regulation in NASH

**Aramchol in Hepatocytes**

- Food Consumption
- ACC
- Serum FA
- Fatty Acid
- Malonyl-Co A
- AMPK
- SCD1
- MUFA
- DG
- TG
- Lipid Droplets
- VLDL
- Serine FA Oxidation
- Fibrosis & Liver Damage

**Aramchol in HSC**

- ARAMCHOL
- SCD1
- ARAMCHOL in Hepatic Stellate cells
- Fz
- LRP
- Wnt
- APC
- GSK3β
- AXIN
- p38
- Ser9
- P
- p

**AMS**

- Food Consumption
- Serum FA
- Fatty Acid
- Malonyl-Co A
- AMPK
- SCD1
- MUFA
- DG
- TG
- Lipid Droplets
- VLDL
- Serine FA Oxidation
- Fibrosis & Liver Damage

**Figure Captions**

- SCDFold Induction
- Relative Gene Expression
- Relative Gene Expression
- Relative Gene Expression
- Relative Gene Expression
- Relative Gene Expression

**Graphs**

- Left: SCD 1 Vehicle
- Right: Aramchol 10µM

**Statistical Symbols**

- *: p < 0.05
- **: p < 0.01
- ***: p < 0.001

**Time Points**

- 48h

**References**

- AASLD
- Liver Meeting
- 2018 San Francisco
- November 9-13

**Abbreviations**

- ACC: Acetyl-CoA Carboxylase
- AMPK: AMP-activated Protein Kinase
- SCD: Stearoyl-CoA Desaturase
- MUFA: Monounsaturated Fatty Acids
- DG: Diacylglycerol
- TG: Triglyceride
- VLDL: Very Low Density Lipoprotein
- PPAR: Peroxisome proliferator-activated receptor
- GSH/GSSG: Glutathione
- COL1: Collagen Type I
- α-SMA: α-Smooth Muscle Actin
- p38: Mitogen-activated protein kinase
- Ser9: Serine 9 phosphorylation
- TGF-β: Transforming Growth Factor-beta
- TGF-RII: Type II TGF-β receptor
- AXIN: Axin
- APC: Adenomatous Polyposis Coli
- Wnt: Wingless-type MMTV Integration Site Family, Member 1
- Fz: Frizzled family member
- LRP: Low-density lipoprotein receptor
- *: p < 0.05
- **: p < 0.01
- ***: p < 0.001
ARREST: A one year global phase 2b randomized placebo-controlled trial

247 patients  57 sites  11 countries

Baseline: MR spectroscopy and centrally-read biopsy

Placebo (N=48)
Aramchol 400 mg (N=101)
Aramchol 600 mg (N=98)

2:2:1

End of treatment: MR spectroscopy and centrally-read biopsy

52 weeks

13 weeks follow up

Screening
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

247 Pts
Randomized and included in ITT

Placebo
N= 48

41 (85.4%) completed 52 weeks + follow-up
7 Early Termination
• 2 - Adverse Event

Paired biopsies 40 (83.3%)

Paired MRS 41 (85.4%)

Aramchol 400
N=101

90 (89.1%) completed 52 weeks + follow-up
11 Early Termination
• 3 - Adverse Event

80 (79.2%)

Aramchol 600
N=98

88 (89.8%) completed 52 weeks + follow-up
10 Early Termination
• 4 - Adverse Event

78 (79.6%)

83 (84.7%)
## Baseline characteristics

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

Mean absolute change from baseline in liver fat

- Placebo (N=41)
- Aramchol 400 (N=90)
- Aramchol 600 (N=83)

Aramchol 400 vs. Pbo  \( p=0.0450 \)
Aramchol 600 vs. Pbo  \( p=0.0655 \)

≥5% ABSOLUTE reduction from baseline

- Placebo (N=41)
- Aramchol 400 (N=90)
- Aramchol 600 (N=83)

Aramchol 600 vs. Pbo  \( p=0.0279 \)
OR 2.77 (95% CI: 1.12-6.89)

Proportion of patients

- Placebo (N=41) 24.4%
- Aramchol 400 (N=90) 36.7%
- Aramchol 600 (N=83) 47%

≥30% RELATIVE reduction from baseline

- Placebo (N=41) 14.6%
- Aramchol 400 (N=90) 25.6%
- Aramchol 600 (N=83) 30.1%

AASLD
American Association for the Study of Liver Diseases

2018 SAN FRANCISCO
NOVEMBER 9-13

11
Results: NASH resolution without worsening of fibrosis

NASH RESOLUTION ALONE:
- Placebo (N=40): 5%
- Aramchol 400 (N=80): 7.5%
- Aramchol 600 (N=78): 16.7%

Aramchol 600 vs. Pbo  p=0.051
OR 4.74 (95% CI: 0.99-22.7)

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

Aramchol 600 vs. Pbo p=0.2110
OR 1.88 (95% CI: 0.70-5.04)

Proportion of patients

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<thead>
<tr>
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<tr>
<td>Proportion</td>
<td>17.5%</td>
<td>21.3%</td>
<td>29.5%</td>
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Progression to Cirrhosis

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<tr>
<td>Proportion</td>
<td>3/40 (7.5%)</td>
<td>6/80 (7.5%)</td>
<td>1/78 (1.3%)</td>
</tr>
</tbody>
</table>
Change from baseline in ALT and AST

**Change from Baseline in ALT (U/L)**

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Week 40</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Aramchol 400 mg</td>
<td>Aramchol 600 mg</td>
</tr>
<tr>
<td>-15.0</td>
<td>-20.0</td>
<td>-25.0</td>
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</table>

Aramchol 400 vs. Pbo : p<0.001
Aramchol 600 vs. Pbo : p<0.0001

**ALT normalization, %**

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<tr>
<td>13.3</td>
<td>21.9</td>
<td>29</td>
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</table>

**Change from Baseline in AST (U/L)**

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Aramchol 400 vs. Pbo : p=0.001
Aramchol 600 vs. Pbo : p<0.0001

**AST normalization, %**

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</thead>
<tbody>
<tr>
<td>4.4</td>
<td>18.8</td>
<td>22.6</td>
</tr>
</tbody>
</table>
Change from baseline in HbA1c

Week 52 Analyses
Aramchol 400 vs. Pbo: p=0.006
Aramchol 600 vs. Pbo: p<0.001
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)

<table>
<thead>
<tr>
<th>Adverse event N (%)</th>
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<tbody>
<tr>
<td>Constipation</td>
<td>6 (12.5)</td>
<td>5 (5)</td>
<td>8 (8.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (8.3)</td>
<td>4 (4)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8.3)</td>
<td>8 (7.9)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (12.5)</td>
<td>14 (13.9)</td>
<td>15 (15.3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2 (4.2)</td>
<td>8 (7.9)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (12.5)</td>
<td>10 (9.9)</td>
<td>9 (9.2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (6.3)</td>
<td>7 (6.9)</td>
<td>11 (11.2)</td>
</tr>
<tr>
<td>UTI</td>
<td>3 (6.3)</td>
<td>15 (14.9)</td>
<td>13 (13.3)</td>
</tr>
</tbody>
</table>
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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- Oren Shibolet, Tel Aviv
- Efrat Broide, Beer Yaakov
In Memoriam of **Prof. Tuvia Gilat, MD 1931-2011**

Visionary of Aramchol