Aramchol™ for NASH

From Scientific Rationale to Clinical Development

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Board of Directors, Galmed Pharmaceuticals
Disclosures

- Member, Board of Directors, Galmed Pharmaceuticals
- Chair, Scientific Advisory Board, ContraVir Pharmaceuticals
- Consultant: Dynavax Technologies, Assembly, Cirius, 3V-BIO. Frazier, Allergan (formerly Tobira), Chimerix
Aramchol™ (arachidyl-amido cholanoic acid) is based on 25 years of R&D by the late Professor Tuvia Gilat, leading the development of a new class of Fatty Acid Bile Acid Conjugates (FABACs)

- Novel synthetic small molecule
- Originally developed for dissolving gallstones
- Orally bioavailable, once daily, tablet formulation
- Aramchol exerts its clinical effect via down regulation of SCD - 1
Aramchol™
Dual MoA Targeting Two Key Pathways of NASH Pathophysiology

**Steatosis**
- Reducing intrahepatic FA and improvement of FA oxidation

**Direct Effect on Liver Fibrosis**
- Reducing proliferation of stellate cells and collagen production

**Liver Fibrosis**

**Prevention and Reversal**
Down Regulation of SCD – 1

- Stearoyl-CoA desaturase (SCD-1) catalyzes the rate limiting step in the biosynthesis of monounsaturated fatty acids and therefore is considered a potent mechanism in liver steatosis and fibrosis

- Down regulation of SCD – 1
  - Reduced body adiposity
  - Increased energy expenditure
  - Upregulation of GSH production, enhancing fatty acid oxidation and maintain redox homeostasis
  - Reduced fibrogenesis in liver including AMPK (5’adenosine monophosphate-activated protein kinase) and SIRT (sirtuin-1)

Data Demonstrating Beneficial Effect of Aramchol™ on NASH
Aramchol’s effect on key histological features has been demonstrated in numerous pre-clinical models of NASH and fibrosis

- High fat diet (HFD) induced steatosis and ballooning
- Methionine and choline deficient (MCD) diet induced aminotransferase elevation and changes in hepatic histological features characterized by steatosis, local inflammation, hepatocyte necrosis and fibrosis
- COL1A1 expression in LX-2 human hepatic stellate cells (in vitro)
- Liver fibrosis induced by intraperitoneal injections of thioacetamide (TAA), to evaluate the direct anti-fibrotic effect
MCD Study Design

Mice were fed the Methionine and Choline Deficient (MCD) and control diet and were sacrificed after 4 weeks. The MCD diet induces aminotransferase elevation and changes in hepatic histological features, characterized by steatosis, local inflammation, hepatocyte necrosis and fibrosis. These changes occur rapidly and are morphologically close to those observed in human NASH.

In this study the MCD diet contained 0.1% methionine to minimize and stabilize weight loss. At the end of the second week, after verification of established NASH, 0.1MCD-fed mice were treated orally by gavage with Aramchol™ (5 mg/Kg/day) or vehicle (n=10, each condition). Control diet-fed mice were also treated with vehicle for same duration (n=10). At the end of the experiment, blood and liver samples were obtained.

**EXPERIMENTAL DESIGN**

<table>
<thead>
<tr>
<th>0.1MCD diet</th>
<th>0.1MCD diet + Aramchol™ 5mg/kg or Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 days</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td>28 days</td>
</tr>
</tbody>
</table>
Effect of Aramchol™ on Liver Steatosis

0.1 MCD Diet by Histology - Sudan III

Treatment with Aramchol™ significantly down regulates steatosis in the liver

Iruarrizaga-Lejarreta et al, Role of aramchol in steatohepatitis and fibrosis in mice, Hepatology Communications 2017
Effect of Aramchol™ on Macrophage Activation and Infiltration

0.1MCD Diet [F4/80 (mouse macrophage) and CD64]

Treatment with Aramchol™ significantly down regulates/normalizes infiltration and activation status of macrophages in the liver

Iruarrizaga-Lejarreta et al, Role of aramchol in steatohepatitis and fibrosis in mice, Hepatology Communications 2017
Treatment with Aramchol™ significantly decreases fibrosis in the liver

Iruarrizaga-Lejarreta et al, Role of aramchol in steatohepatitis and fibrosis in mice, Hepatology Communications 2017
Effect of Aramchol™ on Collagen Production Liver Extract

0.1 MCD Mice

Aramchol™ significantly down regulates collagen in the liver

Iruarrizaga-Lejarreta et al, Role of aramchol in steatohepatitis and fibrosis in mice, Hepatology Communications 2017
Aramchol™ significantly upregulates Glutathione and elevates GSH/GSSG ratio.

Iruarrizaga-Lejarreta et al, Role of aramchol in steatohepatitis and fibrosis in mice, Hepatology Communications 2017
Effect of Aramchol™ on Collagen Production in LX-2 Human HSC

LX-2 Human Hepatic Stellate Cells (HSC)

Aramchol™ significantly down regulates collagen production in LX-2 human HSC

Iruarrizaga-Lejarreta et al, Role of aramchol in steatohepatitis and fibrosis in mice, Hepatology Communications 2017
Liver fibrosis was induced by intraperitoneal injections of TAA (100mg/ml) at a dose of 20mg/100g body weight twice weekly for up to 10 weeks. Rats were treated orally by gavage with Aramchol™ (1 and 5 mg/kg/day) or vehicle. Control TAA induced fibrosis were also treated with vehicle for the same duration. At the end of the experiment, liver samples were obtained. A histological assessment of the livers was performed after staining with hematoxylin-eosin (H&E) and Mason trichrome staining. Evaluation of fibrosis was based on the Ludwig and Batts staining system using the following parameters: portal fibrosis (stage 1) characterized by mild fibrous expansion of portal tracts; peri-portal fibrosis (stage 2) showing fine strands of connective tissue in Zone 1 with only rare portal-portal septa; septal fibrosis (stage 3) manifested by connective tissue bridges that link portal tracts with other portal tracts and central veins but not regenerative nodules; and cirrhosis (stage 4) showing bridging and nodular regeneration.
Effect of Aramchol™ on Fibrosis in the TAA Model

Treatment with Aramchol™ significantly prevents TAA-induced fibrosis

Reif et al, The Anti-Fibrotic Effect of Aramchol on Liver Fibrosis in TAA Animal Model, EASL 2017 poster SAT-454
Aramchol™ Reduces Key Steps in the Pathophysiology of NASH

Metabolism (Steatosis)

Cell stress

Apoptosis

Inflammation

Metabolism (Steatosis)

Collagen Production (Fibrosis)

De-compensated Cirrhosis/ HCC

Pathophysiology of NASH

PPARs
GLP-1
FXR
FGF21

Vitamin E

CCR2-CCR5

Galectin

ARAMCHOL™

ASK1
Caspase
A Phase 2, Multicenter, Double-blind, Randomized, Placebo-Controlled Study on the Effect of Aramchol™ on Liver Triglycerides Concentration in Patients with Steatosis due to Non Alcoholic Fatty Liver Disease (NAFLD) or Non Alcoholic Steatohepatitis (NASH)*

<table>
<thead>
<tr>
<th>Design:</th>
<th>Multicenter (12, Israel, randomized, double-blind, placebo-controlled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants:</td>
<td>Patients with NAFLD or NASH</td>
</tr>
<tr>
<td>Doses:</td>
<td>• 100 mg; 300 mg; Placebo</td>
</tr>
<tr>
<td></td>
<td>• 1:1:1</td>
</tr>
<tr>
<td>Treatment Plan:</td>
<td>Once-daily tablet for 12 weeks and 4 weeks follow-up</td>
</tr>
<tr>
<td>Number of Subjects:</td>
<td>60 patients</td>
</tr>
<tr>
<td>Primary Endpoint:</td>
<td>Reduction in liver fat concentration measure by MRS</td>
</tr>
<tr>
<td>Secondary Endpoints:</td>
<td>Liver and metabolic biomarkers levels</td>
</tr>
</tbody>
</table>

* Safadi et al. Aramchol Reduces Liver Fat Content in Patients With Nonalcoholic Fatty Liver Disease, Clinical Gastroenterology and Hepatology, June 2014
Phase 2a Efficacy and Safety

Percent relative change in liver TG levels, baseline and end of treatment

Overall and most frequent events
(> 2 patients in any group)

<table>
<thead>
<tr>
<th></th>
<th>Aramchol 300 mg N = 20 n (%)</th>
<th>Aramchol 100 mg N = 20 n (%)</th>
<th>Placebo N = 20 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AE(s)</td>
<td>9 (45.0)</td>
<td>8 (40.0)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>Preferred term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Abdominal upper pain</td>
<td>2 (10.0)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>-</td>
<td>-</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>-</td>
<td>-</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>-</td>
<td>-</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (10.0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Similar frequency of adverse events in all treatment groups
- Adverse events were mild or moderate, none were serious
- None of the patients withdrew as a result of adverse events

300 mg Aramchol™ demonstrated statistically significant liver fat content reduction
# Phase 2b Study

**ARREST (ARamachol™ for RESolution of Steatohepatitis)**

A Phase 2b, double blind randomized, controlled clinical trial, to evaluate the efficacy and safety of two Aramchol™ doses versus placebo in patients with Non-Alcoholic Steatohepatitis (NCT 02279524)

<table>
<thead>
<tr>
<th>Design:</th>
<th>Multicenter, randomized, double-blind, placebo-controlled, dose ranging study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants:</td>
<td>Biopsy-diagnosed (centrally read) NASH patients with obesity and insulin resistance</td>
</tr>
</tbody>
</table>
| Doses: | • 400 mg; 600 mg; Placebo  
• 2:2:1 |
| Treatment Plan: | 12 months treatment (once daily tablet) and 3 months of follow-up |
| Number of Subjects: | 248 patients |
| Primary Endpoint: | Reduction in liver fat content measured by MRS |
| Secondary Endpoints: | Biopsy: fibrosis improvement; > 2 point NAS improvement; NASH resolution; Metabolic markers |

![Timeline of the study](image_url)

**Biopsy (up to 6 months before randomization)**

**Screening**  
45 days  
MRI  

**Randomization**  
400 mg  
600 mg  
Placebo  

**Follow-up**  
52 weeks  
MRS  
Biopsy  

13 weeks
ARREST Key Inclusion Criteria

- BMI between 25kg/m² to 40kg/m² or waist circumference between 88cm to 200cm for women, and between 102cm to 200cm for men

- Known Type 2 Diabetes Mellitus or pre-Diabetes according to American Diabetes Association. One of the following 3 criteria is needed for pre-Diabetes: Fasting Plasma Glucose > 100mg/dl (5.5 mmol/l) or 2hPG following 75g OGTT > 140 (7.8 mmol/l) mg/dl or HbA1c > 5.7%

- Histologically proven Steatohepatitis on a diagnostic liver biopsy performed either during Screening or within 6 months before screening visit, confirmed by central laboratory reading of the slides (steatosis ≥1 + inflammation ≥1 + ballooning ≥1). Total activity NAS score of 4 or more
  - Central reading performed by Prof. Carolin Lancker 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-Baasat at the Sourasky Medical Center, Israel
ARREST Primary and Secondary Endpoints

Primary end-point

• Percent (%) change from baseline to end of study in liver triglycerides ratio (relative to water) as measured by MRS

Key secondary end-points

• Proportion (%) of subjects with CRN Fibrosis Score Improvement without worsening of NASH
• Proportion (%) of subjects with NAS Score Improvement (>2 points) without worsening of CRN Fibrosis Score
• Proportion (%) of subjects with SAF Activity Score Improvement (>2 points) without worsening of CRN Fibrosis Score
• Proportion (%) of subjects with NASH Resolution (ballooning 0; inflammation 0 or 1) without worsening of CRN Fibrosis Score
• Change from Baseline to Week 52/Termination in ALT
## ARREST Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All Subjects (N=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>160 (64.8%)</td>
</tr>
<tr>
<td>Age years (mean +SD)</td>
<td>54.4 +10.3</td>
</tr>
<tr>
<td>Weight kg (mean +SD)</td>
<td>87.7 +16.8</td>
</tr>
<tr>
<td>BMI (kg/m2) (mean +SD)</td>
<td>32.7 +4.4</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Hispanic/Latin/Latin American/Martinican</td>
<td>79 (31.9%)</td>
</tr>
<tr>
<td>White</td>
<td>155 (62.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study ARREST-005</th>
<th>Mean +SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT U/L</td>
<td>62.8 +44.3</td>
</tr>
<tr>
<td>AST U/L</td>
<td>46.7 +33.1</td>
</tr>
<tr>
<td>CHOLESTEROL mmol/L</td>
<td>4.79 +1.17</td>
</tr>
<tr>
<td>HDL CHOLESTEROL mmol/L</td>
<td>1.19 +0.33</td>
</tr>
<tr>
<td>LDL DIRECT mmol/L</td>
<td>2.98 ± 0.98</td>
</tr>
<tr>
<td>TRIGLYCERIDES mmol/L</td>
<td>1.95 +1.33</td>
</tr>
<tr>
<td>GLUCOSE PLASMA mmol/L</td>
<td>6.71 +1.98</td>
</tr>
<tr>
<td>HEMOGLOBIN A1C (%)</td>
<td>6.59 +0.97</td>
</tr>
</tbody>
</table>
70% of patients have NAS $\geq$ 5

NAS = NAFLD Activity Score, ranges from 0-8 and is composed of the unweighted sum of three histological components: steatosis (0-3), lobular inflammation (0-3) and ballooning degeneration (0-2)

60% of patients have fibrosis stage 2 and 3

The Clinical Research Network (CRN) Pathology Committee developed a scoring system using NASH activity (Grade) and collagen deposition plus architectural remodeling (Stage)
<table>
<thead>
<tr>
<th>Population</th>
<th>Inclusion</th>
<th>Baseline mean NAS</th>
<th>Baseline mean fibrosis</th>
<th>Number of patients</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NASH without diabetes</td>
<td>4.9</td>
<td>1.5</td>
<td>247</td>
<td>96 weeks</td>
</tr>
<tr>
<td></td>
<td>NASH with NAS≥4</td>
<td>5.1 - 5.3</td>
<td>1.8 - 1.9</td>
<td>283 ; ITT 219</td>
<td>72 weeks</td>
</tr>
<tr>
<td></td>
<td>NASH with NAS≥3</td>
<td>4.9 - 5</td>
<td>1.5 - 1.7</td>
<td>274</td>
<td>52 weeks</td>
</tr>
<tr>
<td></td>
<td>NASH + enriched population</td>
<td>5.3</td>
<td>2.1</td>
<td>289</td>
<td>52 weeks</td>
</tr>
<tr>
<td></td>
<td>NASH + obesity and insulin resistance</td>
<td>5</td>
<td>2</td>
<td>248</td>
<td>52 weeks</td>
</tr>
</tbody>
</table>

**Comparison to Other Leading Phase 2b Studies**

- **PIVENS**
  - NASH without diabetes
  - Baseline mean NAS: 4.9
  - Baseline mean fibrosis: 1.5
  - Number of patients: 247
  - Duration: 96 weeks

- **FLINT**
  - NASH with NAS≥4
  - Baseline mean NAS: 5.1 - 5.3
  - Baseline mean fibrosis: 1.8 - 1.9
  - Number of patients: 283 (ITT 219)
  - Duration: 72 weeks

- **GOLDEN**
  - NASH with NAS≥3
  - Baseline mean NAS: 4.9 - 5
  - Baseline mean fibrosis: 1.5 - 1.7
  - Number of patients: 274
  - Duration: 52 weeks

- **CENTAUR**
  - NASH + enriched population
  - Baseline mean NAS: 5.3
  - Baseline mean fibrosis: 2.1
  - Number of patients: 289
  - Duration: 52 weeks

- **ARREST**
  - NASH + obesity and insulin resistance
  - Baseline mean NAS: 5
  - Baseline mean fibrosis: 2
  - Number of patients: 248
  - Duration: 52 weeks
ARRIVE (Aramchol™ versus placebo in the treatment of HIV-associated nonalcoholic fatty liver disease and lipodystrophy): A randomized, double-blinded, allocation-concealed, placebo controlled clinical trial.

An investigator-initiated study conducted at the NAFLD Research Center, University of California San Diego by Professor Rohit Loomba. NCT02684591 under IND

<table>
<thead>
<tr>
<th>Design:</th>
<th>Single center, randomized, double-blind, placebo-controlled, proof of concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants:</td>
<td>Patients with HIV-associated NAFLD</td>
</tr>
</tbody>
</table>
| Doses: | • Placebo (25 patients)  
       | • 600 mg (25 patients) |
| Treatment Plan: | Once-daily tablet for 12 weeks |
| Number of Subjects: | 50 patients |
| Primary Endpoint: | Hepatic steatosis assessed by MRI-PDFF |
| Secondary Endpoints: | MRE, Total body fat, metabolic profile, and liver biochemistry |

Study completion expected Feb 2018
Summary

- Aramchol™ is an SCD1 modulator that has shown a significant effect on the 3 key pathologies of NASH (steatosis, inflammation and fibrosis) in several pre-clinical models.
- The effect on fibrosis is both indirect, through reduction of steatosis, and direct through reducing stellate cell proliferation and collagen production.
- The effect on steatosis has been demonstrated in humans in a Phase 2a study with a significant reduction in liver fat demonstrated by MRS.
- The ARRIVE study in HIV-associated NAFLD and lipodystrophy scheduled to read out in Q1 2018.
- The ongoing Phase 2b Study ARREST enrolled a population with severe NASH and is expected to read out in Q2 2018.
- An end of Phase 2 meeting will be held with the FDA in 2018, prior to initiation of Phase 3.
Aramchol™ for NASH and Beyond: From Scientific Rationale to Clinical Development
Thank You