Aramchol Meglumine- Novel, First-in-class, Phase 3, Anti-fibrotic Agent

Primary sclerosing cholangitis (PSC) Strategic Plan

May 2023

Galmed Pharmaceuticals

Galmed Pivots from NASH as main Indication

- Despite strong positive results in the Open Label part of ARMOR Phase 3 study, Galmed has paused in NASH until the FDA and Market show clear guidelines for endpoints and interest
- Data accumulated in patients with NASH enables quick transition to Phase 2/3 clinical studies in other fibro-inflammatory indications with high unmet need and expedited regulatory pathways
- Direct anti-fibrotic efficacy is supported by animal studies in other organs: lung, skin, kidney & GI
- Primary sclerosing cholangitis (PSC) is an orphan disease that has no treatment
- A short Phase 2 study in collaboration with the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health Virginia Commonwealth University is planned to be initiated in Q4 2023
- The study will examine the safety and efficacy of Aramchol in patients with PSC, who may also have inflammatory bowel disease (IBD).
- Aramchol Meglumine is an improved version of Aramchol with NCE patent status up to 2035 (fibrosis patent up to 2038)

Aramchol Meglumine – A First in Class, Novel, SCD 1 Modulator

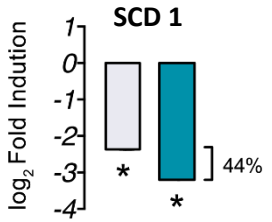
Aramchol Meglumine is a fatty acid bile acid conjugate (FABAC) that inhibits Stearoyl-CoA desaturase 1 (SCD1), a key liver enzyme involved in lipid metabolism

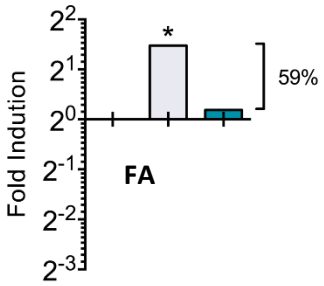
The efficacy and safety of Aramchol have been demonstrated in two multinational Phase 2 studies, and in the Open Label Part of the Phase 3 ARMOR NASH Study

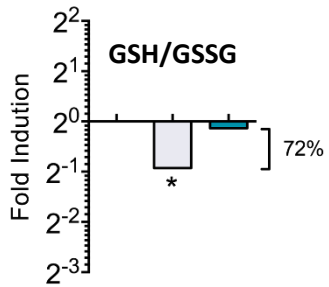
Aramchol MoA has been extensively characterized showing:

- Reduction of liver triglycerides and fibrosis
- Statistically significant anti-fibrotic effect in a liver & lung fibrosis models
- Statistically significant improvement in the dextran sulfate sodium (DSS)-induced colitis IBD model
- Down-regulation of liver fatty acids (FA) in multiple dietary models

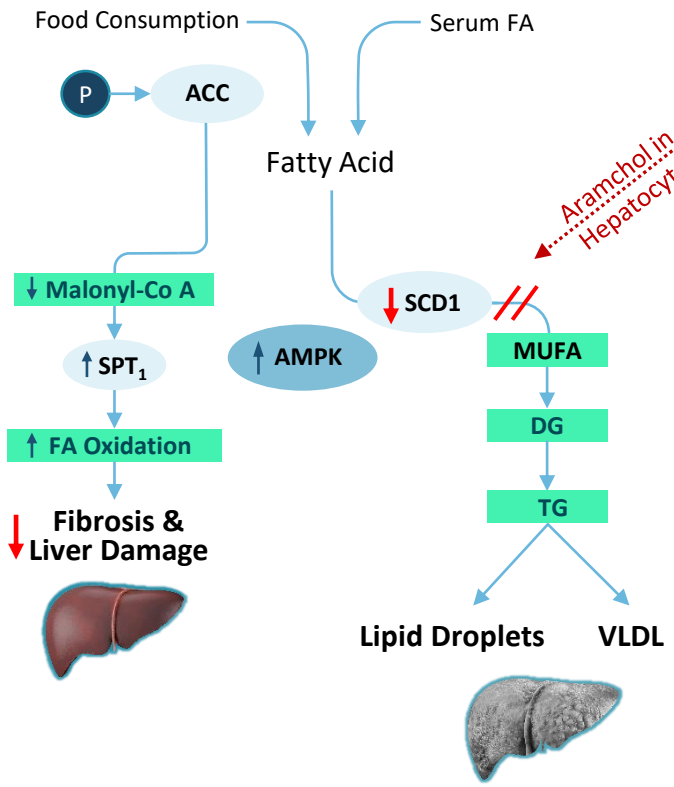
Aramchol in the Liver Reduces Steatosis, Oxidative Stress and Liver Injury

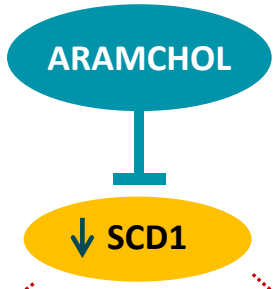






Aramchol in Hepatocytes

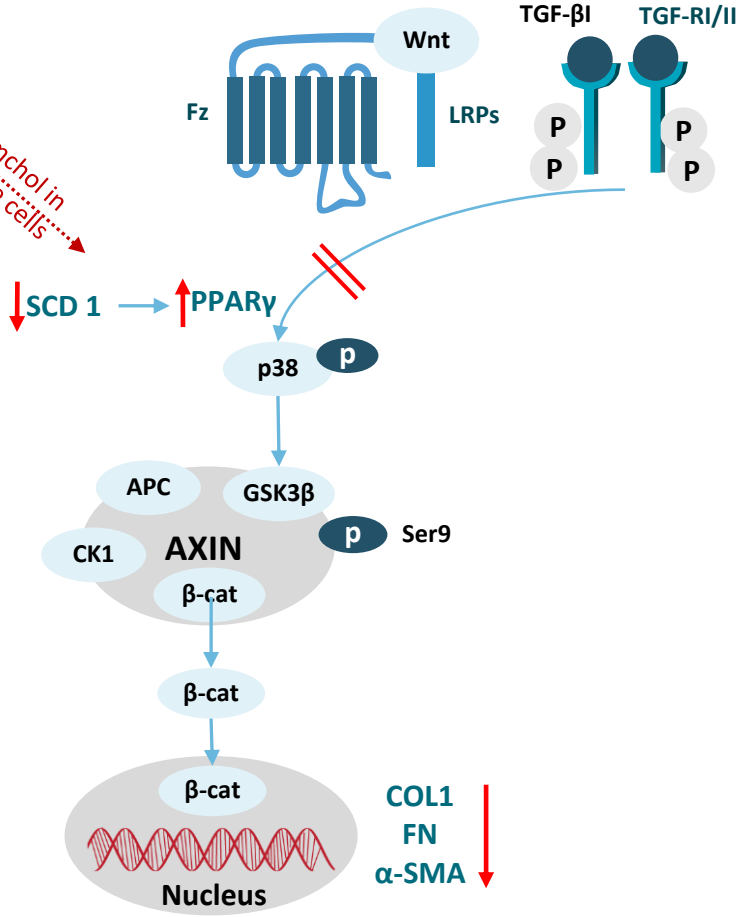


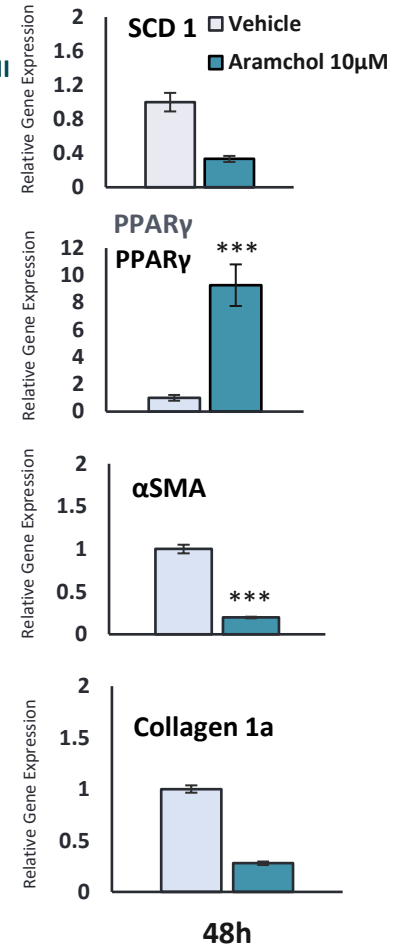


Aramchol in Hepatocytes

Aramchol in Stellate cells

Aramchol in Hepatic Stellate Cells





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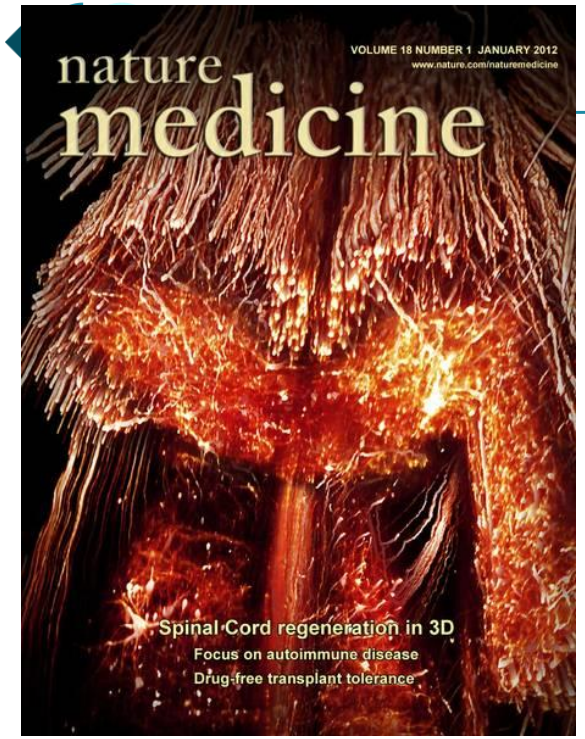

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01495-3

Check for updates

Aramchol in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2b trial

V. Ratziu[1]✉, L. de Guevara[2], R. Safadi[3], F. Poordad[4], F. Fuster[5], J. Flores-Figueroa[6], M. Arrese[7], Anna L. Fracanzani[8], D. Ben Bashat[9], K. Lackner[10], T. Gorfine[11], S. Kadosh[12], R. Oren[11], M. Halperin[11], L. Hayardeny[11], R. Loomba[13], S. Friedman[14], the ARREST investigator study group* and Arun J. Sanyal[15]

the ARREST investigator study group

M. Abdelmalek[16], F. Angelico[17], M. Angelico[18], J. P. Arancibia[19], E. Bardou-Jacquet[20], F. Barrera[21], C. F. Barish[22], Y. Baruch[23], Z. Ben-Ari[24], T. Berg[25], M. Bourliere[26], J. Boursier[27], E. Broide[28], M. Carmiel[29], D. S. Denham[30], L. Di Cesare[31,32], D. L. Dumitrascu[31,32], A. Francis[33], S. Gawrieh[34], M. S. González- Huezo[35], P. Hillon[36], A. Iracheta[37], Z. Kayali[38], L. Kupcinskas[39], G. Lau[40], L. Serfaty[41], A. Le Cleach[41], C. Loguercio[42], M. Manns[43], B. I. Martinez Saldivar[44], E. A. Mena[45], L. A. Morales Garza[46], J. M. Neutel[47], L. Nikoleishvili[48], M. Noureddin[49], R. Pais[50], A. H. Paredes[51], M. Paredes[52], R. Peters Watkins[53], A. Picardi[54], M. Pirisi[55], G. P. Jofre[56], L. Preotescu[57], T. Saadi[23], D. Samuel[58], J. F. Sánchez Avila[59], I. Schiefke[60], O. Shibolet[61], M. S. Siddiqui[15], G. Torres-Mendoza[35], J. F. Trotter[62], E. Tsai[63], E. C. Verna[64], E. Zuckerman[65] and D. Zur[29]

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Summary of Results of the Open-Label Part of the ARMOR Study

- The OL part (N=154) met its objectives demonstrating the potential anti-fibrotic effect of Aramchol 300 mg BID using three different histopathology methodologies, imaging and biomarkers and showed that longer treatment duration results in a larger treatment effect

    - **High proportion of fibrosis improvement across separate and independent 3 biopsy reading methods with a larger treatment effect observed with longer duration of therapy**
    - Highly statistically significant ($p<0.0001$) reduction in Fibroscan
    - Highly statistically significant ($p<0.0001$) reduction in ALT, AST, and FIB-4
    - Highly statistically significant($p<0.0001$) reductions in Pro-C3 at week 24 using two analytical methods and several statistical models
    - A statistically significant ($p= 0.0038$) reduction in ELF at Week 24

- The OL part demonstrated the good and consistent safety profile of Aramchol 300mg BID, including long-term follow up

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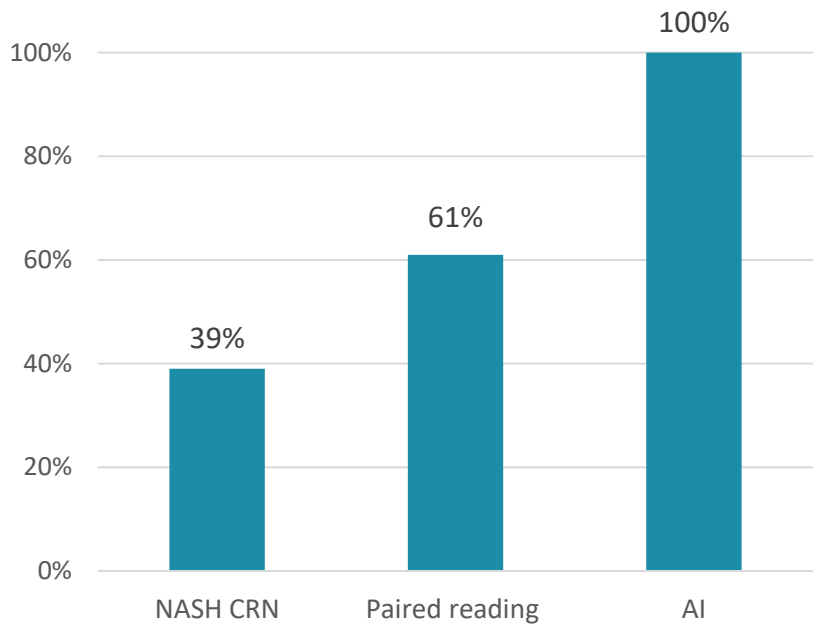
Effect of Aramchol on Fibrosis Using 3 Histopathological Reading Methodologies

Biopsy methodology	Post-BL Biopsy at <W48 weeks		Post-BL Biopsy at ≥ W48	
	N	%	N	%
All	28	100%	23	100%
Fibrosis Improvement (1 point or more) NASH CRN	7	25%	9	**39%**
Fibrosis Improvement (Paired reading)	12	43%	14	**61%**
Subject Fibrosis Response (AI reading*)	15	54%	23	**100%**
Subject Fibrosis Response (AI reading-responder is defined by a relative reduction of 25% or greater)	6	21.4%	15	**65.2%**

* Quantification of change from baseline by AI using Fibronest's Phenotypic FCS demonstrated statistically significant ($p<0.0001$) fibrosis reduction

% Patients with Fibrosis Improvement for Each Reading Methodology after ≥48 weeks



Ratziu et al. Multimodality assessment of hepatic fibrosis: ranked paired reading and artificial intelligence identifies fibrosis improvement with aramchol missed by conventional staging. Journal of Hepatology. 2022;77:S714. doi:10.1016/S0168-8278(22)01745-7

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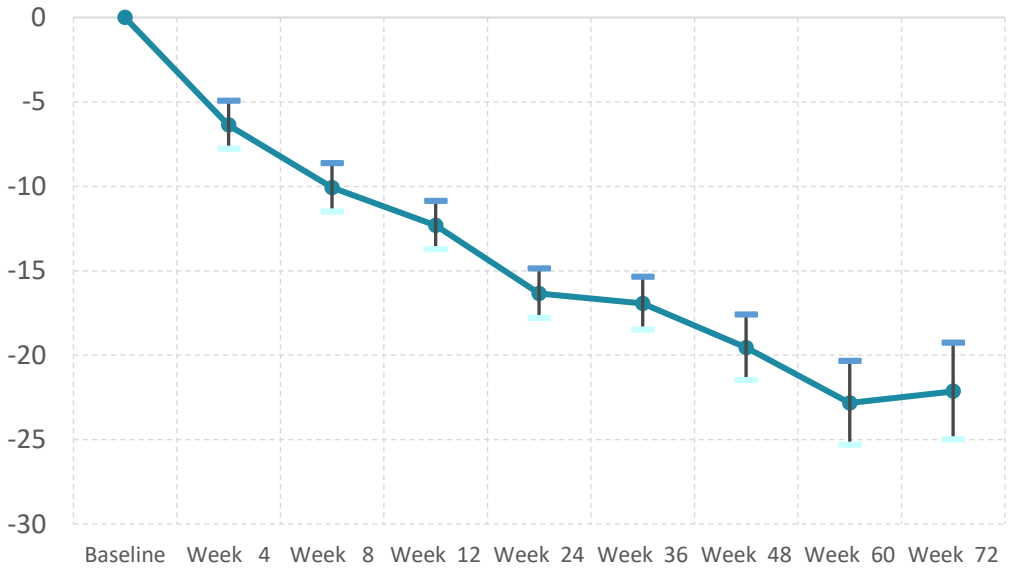
Effect of Aramchol on Liver Enzymes

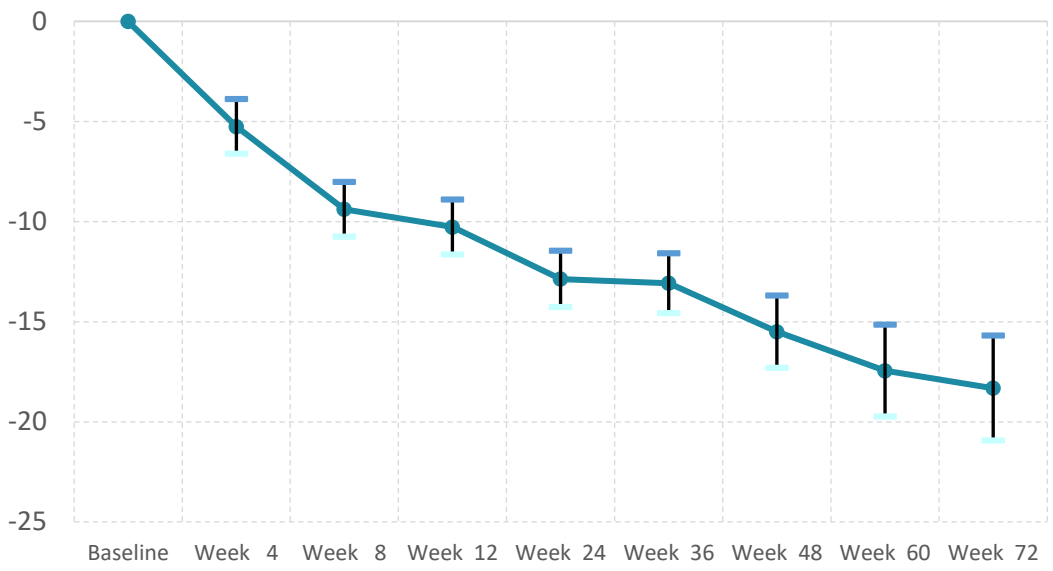
Highly statistically significant (p<0.0001) reductions from baseline in ALT and AST

Baseline-adjusted MMRM analysis in ALT (U/L)



LSM of Change from Baseline ± SE by Visit
Baseline N=154, W24 N=133, W48 N=66, W72 N=27

Baseline-adjusted MMRM analysis in AST (U/L)



LSM of Change from Baseline ± SE by Visit
Baseline N=154, W24 N=133, W48 N=66, W72 N=27

Aramchol Significantly Down Regulates Liver Enzymes – Significant Restoration of Liver Functionality – Data Consistent with Previous Studies

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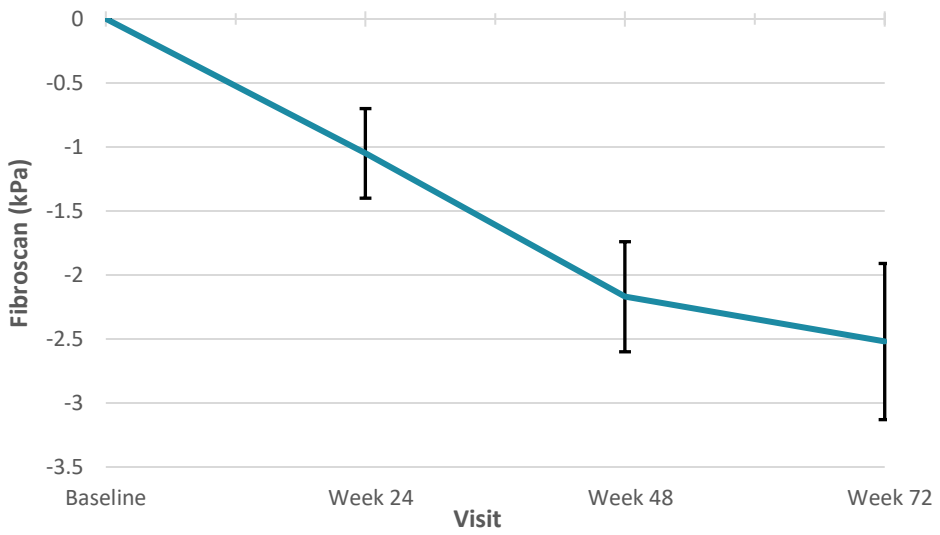
Effect of Aramchol on Fibrosis: Fibroscan Of Patients Participating Open-Label Part of the ARMOR Study

Highly statistically significant (p<0.0001) reductions from baseline in Fibroscan

Baseline-adjusted MMRM analysis in Fibroscan (kPa)



LSM of Change from Baseline ± SE by Visit

Baseline N=139, W24 N=112, W48 N=61, W72 N=26

Aramchol Significantly Down Regulates Liver Fibrosis – Significant Down Regulation in Fibroscan Reading

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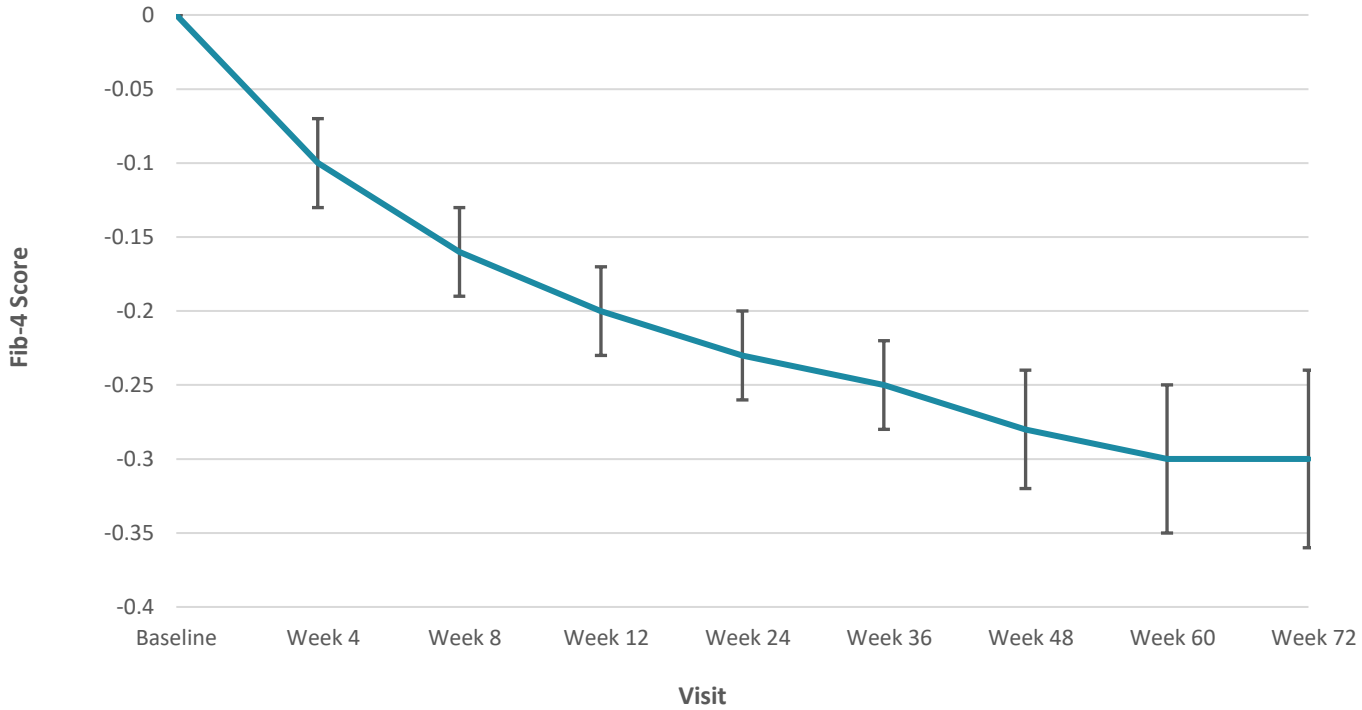
Effect of Aramchol on Fibrosis: Fib-4 bio marker, in Patients Open-Label Part of the ARMOR Study

Highly statistically significant (p<0.0001) reductions from baseline in Fib-4 score

Baseline-adjusted MMRM analysis in Fib-4 score



LSM of Change from Baseline ± SE by Visit

Baseline N=154, W24 N=128, W48 N=64, W72 N=27

Aramchol Significantly Down Regulates Liver Fibrosis – Significant Down Regulation in Fib 4 Bio Marker

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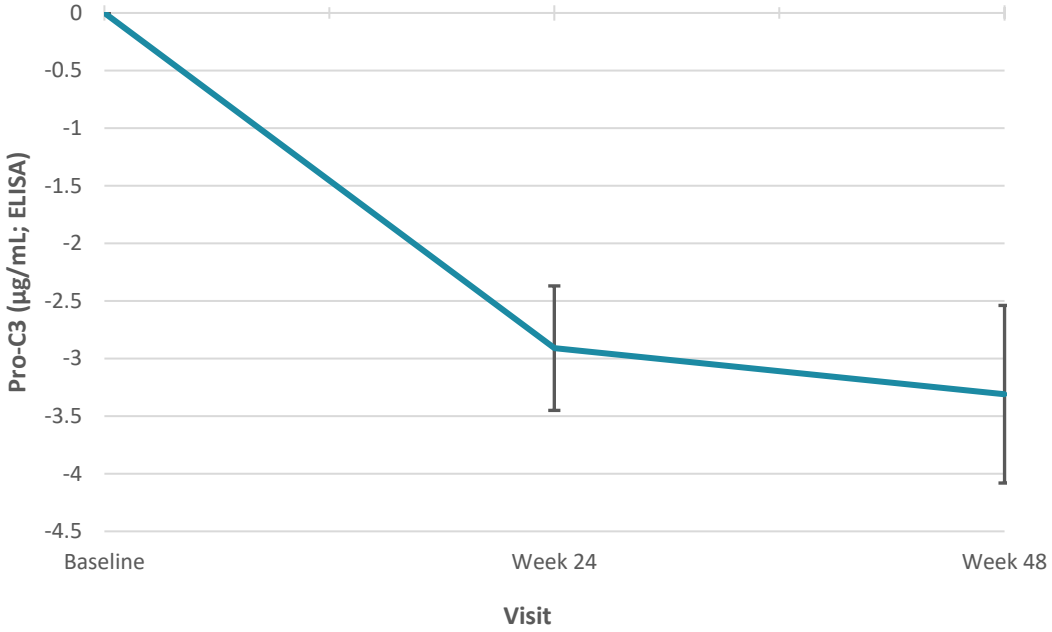
Effect of Aramchol on Fibrosis: Pro-C3 bio marker, in Patients Open-Label Part of the ARMOR Study

Statistically significant reductions in Pro -C3 were noted from baseline to week 24 (p<0.0001) and baseline to week 48 (p=0.0074) using ELISA and based on MMRM analysis

Baseline-adjusted MMRM analysis in Pro-C3 (ng/mL)



LSM of Change from Baseline ± SE by Visit

Baseline N=43, W24 N=43, W48 N=15

Aramchol Significantly Down Regulates Liver Fibrosis – Significant Down Regulation in Pro-C3 Bio Marker

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Excellent Safety and Tolerability Profile in the Phase 3 ARMOR Open-Label Part Study

- Discontinuation due to adverse events remained low and was less than 5%
- SAEs reported in 10.4% of patients; no SAE was atypical for the studied population
- No deaths reported
- No signal for hepatotoxicity was noted
- Assessment of liver enzymes during the study were consistent with efficacy results and showed a low incidence rate of increases

Most frequent AEs (≥5% of subjects)

Adverse event N (%)	Aramchol 300 mg BID (n=154)
Back pain	9 (5.8)
Covid-19	27 (17.5)
Constipation	8 (5.2)
Headache	12 (7.8)
Hypretension	10 (6.5)
Nausea	8 (5.2)
Procedural pain	8 (5.2)

Aramchol Efficacy in Idiopathic Pulmonary Fibrosis (IPF) and Inflammatory Bowel Disease (IBD) Models

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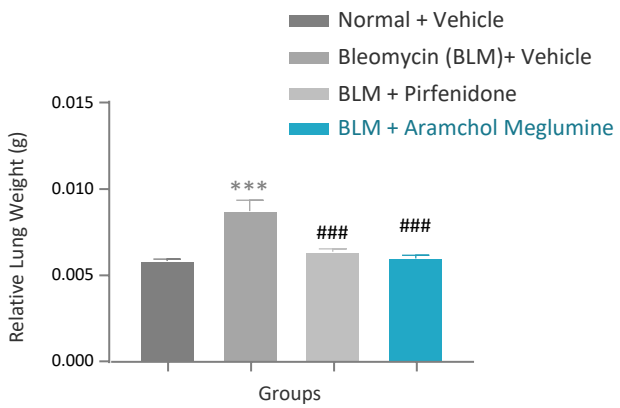
The Effect of Aramchol Meglumine in Pre-clinical Model of Lung Fibrosis

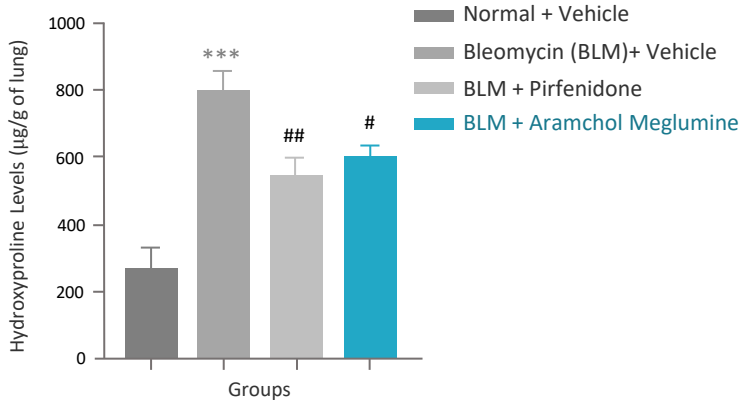
Statistically significant anti-fibrotic effect of Aramchol in the bleomycin mice model of IPF

Lung Weight



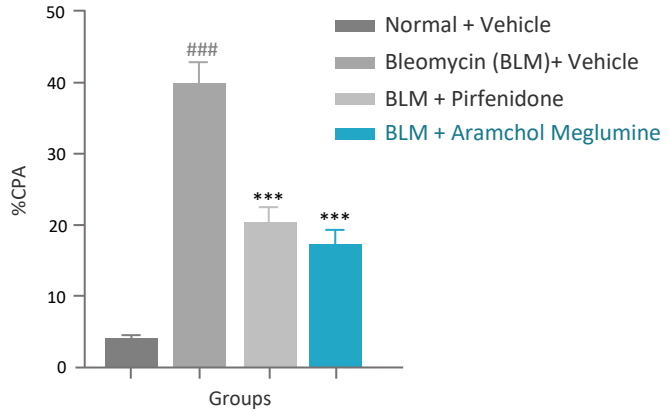
Data indicates Mean ± SEM. ***p<0.001 Vs Normal + Vehicle, ###p<0.001 Vs Bleomycin + Vehicle, one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-12.

Hydroxyproline



Data indicates Mean ± SEM. ***p<0.001 Vs Normal Control, #p<0.05, ## p<0.005 BLM + Vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-12.

% Collagen Proportionate Area



Data indicates Mean ± SEM. ###p<0.001 Vs Normal Control, ***p<0.001 vs BLM + Vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-12.

Aramchol Normalizes Hydroxyproline and Reduces Collagen Proportion Area both Important Indicators for the Severity of Fibrosis in the Lung

Bleomycin model of lung fibrosis, which is the best-characterized and most extensively used animal model due to its ability to reproduce many aspects of IPF and other fibrotic Interstitial lung diseases

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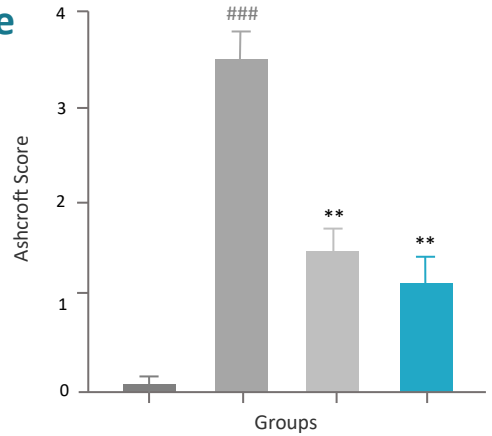
The Effect of Aramchol Meglumine in Pre-clinical Model of Lung Fibrosis (Cont.)

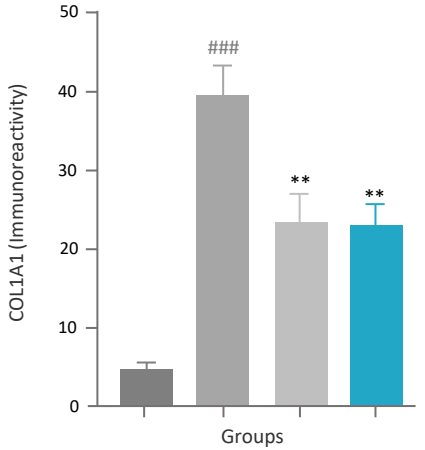
Statistically significant anti-fibrotic effect of Aramchol in the bleomycin mice model of IPF

Ashcroft Score (lung fibrosis)



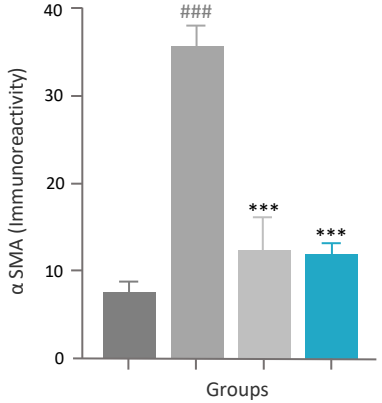
Data indicates Mean±SEM. ###p<0.001 Vs Normal Control, **p<0.005 Vs BLM + Vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-12.

Collagen 1A1



Data indicates Mean±SEM. ###p<0.001 Vs Normal Control, #p<0.05, **p<0.005 vs BLM + Vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-12.

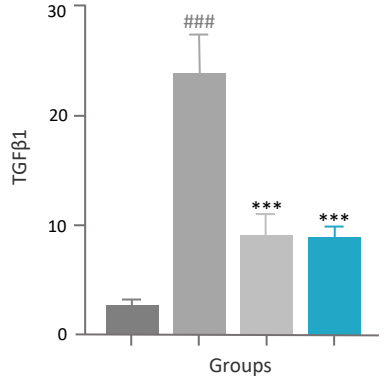
α SMA



Data indicates Mean±SEM. ###p<0.001 Vs Normal Control, **p<0.005 vs BLM + Vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-12.

- Normal + Vehicle
- Bleomycin (BLM)+ Vehicle
- BLM + Pirfenidone
- BLM + Aramchol Meglumine

TGFβ1



Data indicates Mean±SEM. ###p<0.001 Vs Normal Control, **p<0.001 vs BLM + Vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 4-6.

Aramchol significantly Down regulates Ashcroft Score (Fibrosis Score grade 0-8), Collagen 1A1 α SMA, and TGFβ1 Scores and all Markers of Fibrosis are Going in Same Direction, Suggesting Significant Anti Fibrotic Effects.

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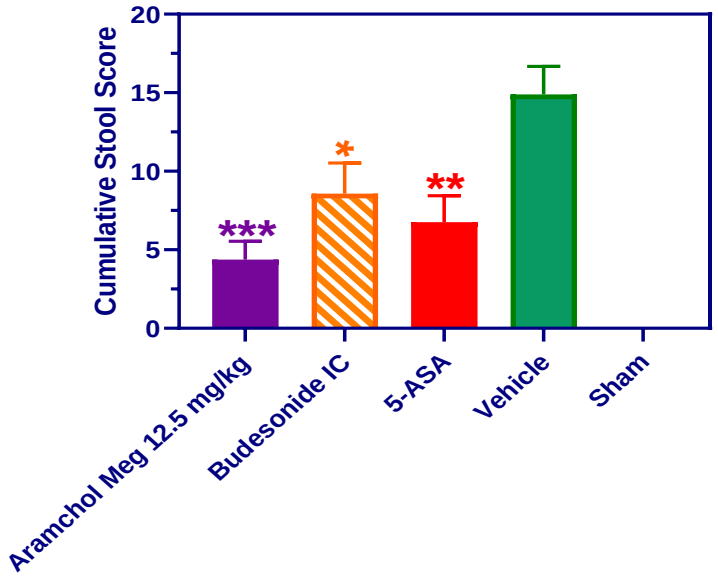
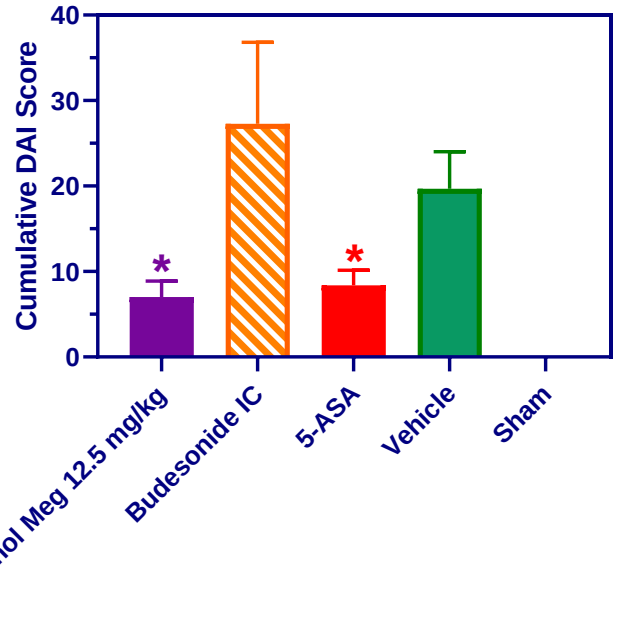
The Effect of Aramchol Meglumine in Pre-clinical Model of Ulcerative Colitis

Statistically significant effect of Aramchol in the Dextran Sulphate Sodium (DSS) mice model of IBD

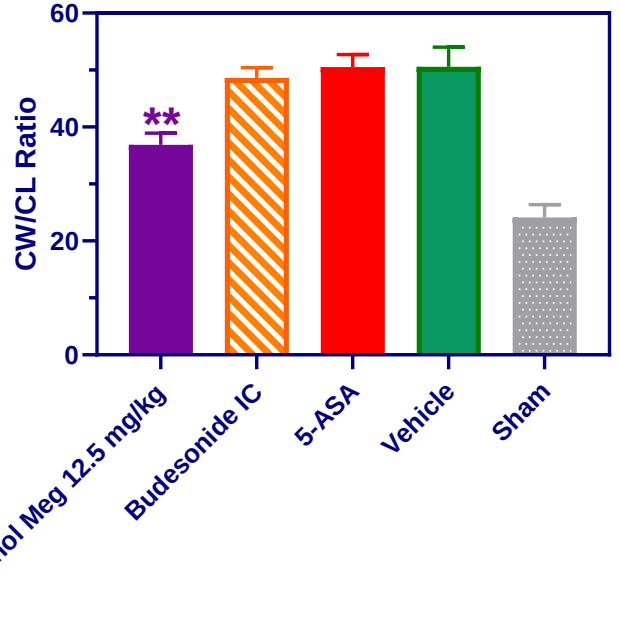
Cumulative Stool Score



Cumulative Disease Activity Index



Colon Weight/Length



n=8-9 mice per treatment group (3 animals for sham group)

* p <0.05 vs Vehicle
** p <0.01 vs Vehicle
*** p <0.001 vs Vehicle
Unpaired t test

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Aramchol & Primary Sclerosing Cholangitis (PSC)

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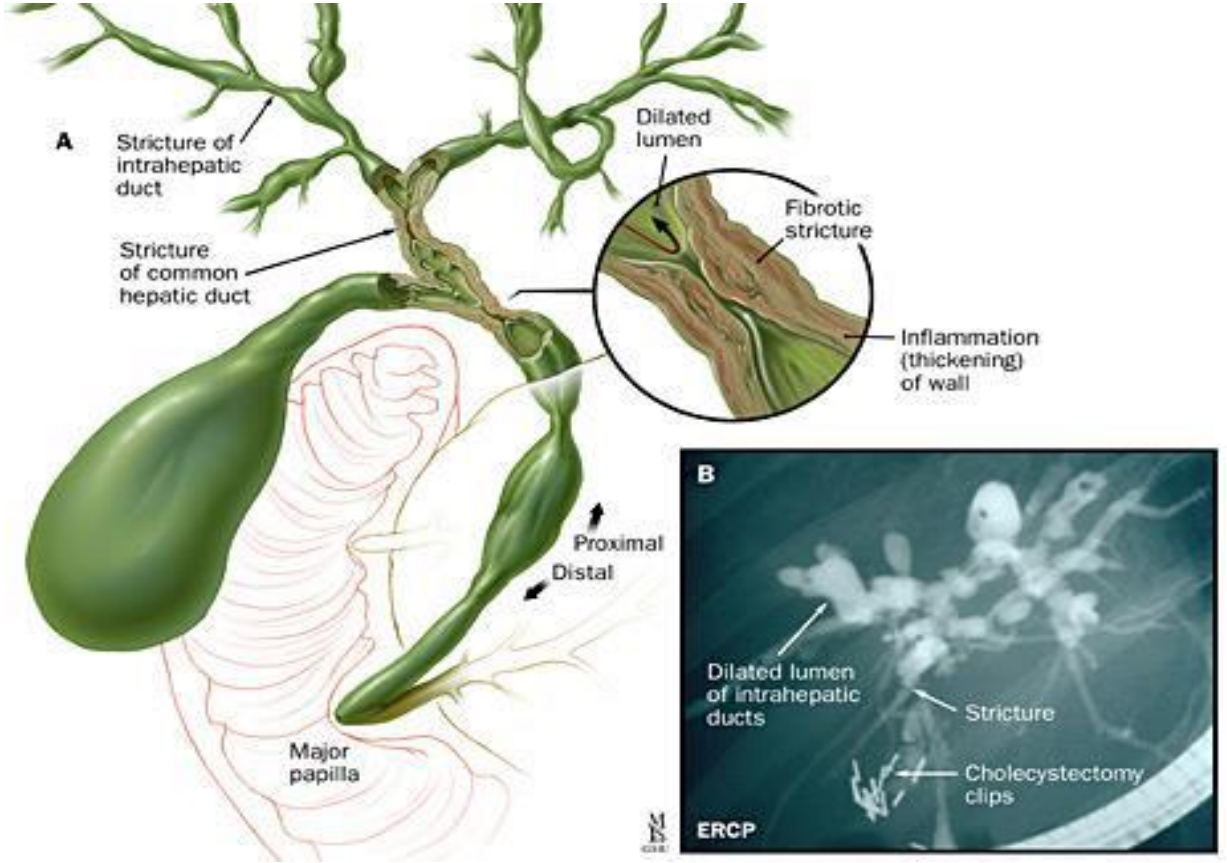
The Bile Duct Walls in Primary Sclerosing Cholangitis (PSC) are Characterized by Inflammation and Scarring

Biliary Tree and Thickening of Walls



- Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic disease that causes inflammation, scarring, and narrowing of the bile duct walls, leading to blockages and bile accumulation in the liver
- This can eventually result in liver damage, cirrhosis, and end-stage liver disease, and may also cause infections
- PSC is a slowly progressing disease with no known cause and is more common in men, especially in Northern European heritage, and is often diagnosed between ages 30-40
- Most cases (~ 70%)[1] occur in association with IBD
- **Treatments are limited to symptom management and monitoring, with liver transplant as an option in severe cases (which could still become recurrent).**

Source: [1] Primary sclerosing cholangitis and inflammatory bowel disease comorbidity: an update of the evidence - PMC (nih.gov) *American Liver Foundation, Harvard Health, Tabibian et al., Gastroenterol 2018, Mayo Clinic, Johns Hopkins*

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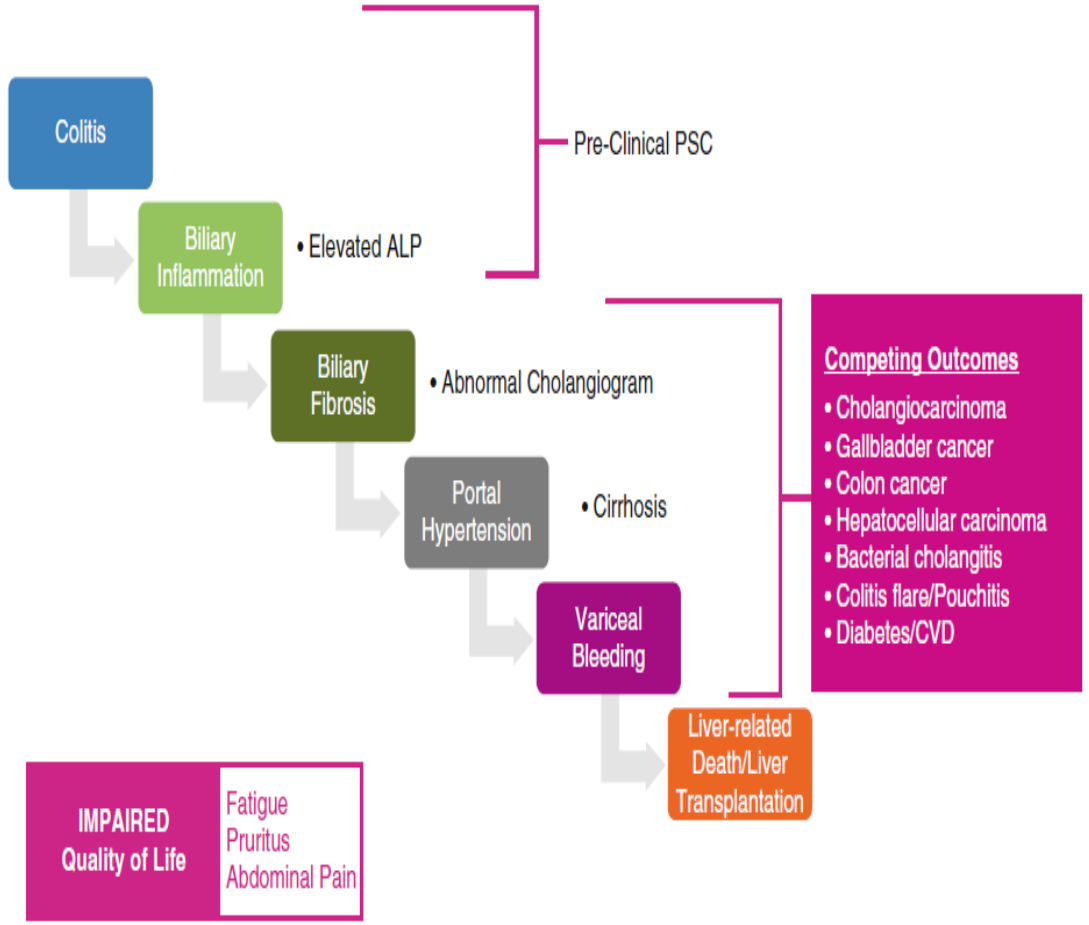
Market- At least 60,000 Patients in US & Western Europe

- Prevalence estimated at 1 per 10,000, suggesting ~33.5k patients in the US and ~ 32.5k in the EU5, with 90% of cases being the classic subtype[1]
- There are no approved drugs for PSC, with a preclinical stage likely involving UC leading to biliary inflammation.
- Potential for Orphan Drug Status
- Biliary fibrosis progresses to cirrhosis and its complications, with competing risks.
- About 50% of patients with PSC report clinical symptoms[2]



Source: DOI 10.1007/978-3-319-40908-5_1, Company Releases, J Hepatol . 2017 Dec;67(6):1298-1323, Johns Hopkins

[1] Global incidence, prevalence and features of primary sclerosing cholangitis: A systematic review and meta-analysis - PubMed (nih.gov)

2 https://doi.org/10.1016/j.gastro.2003.07.011

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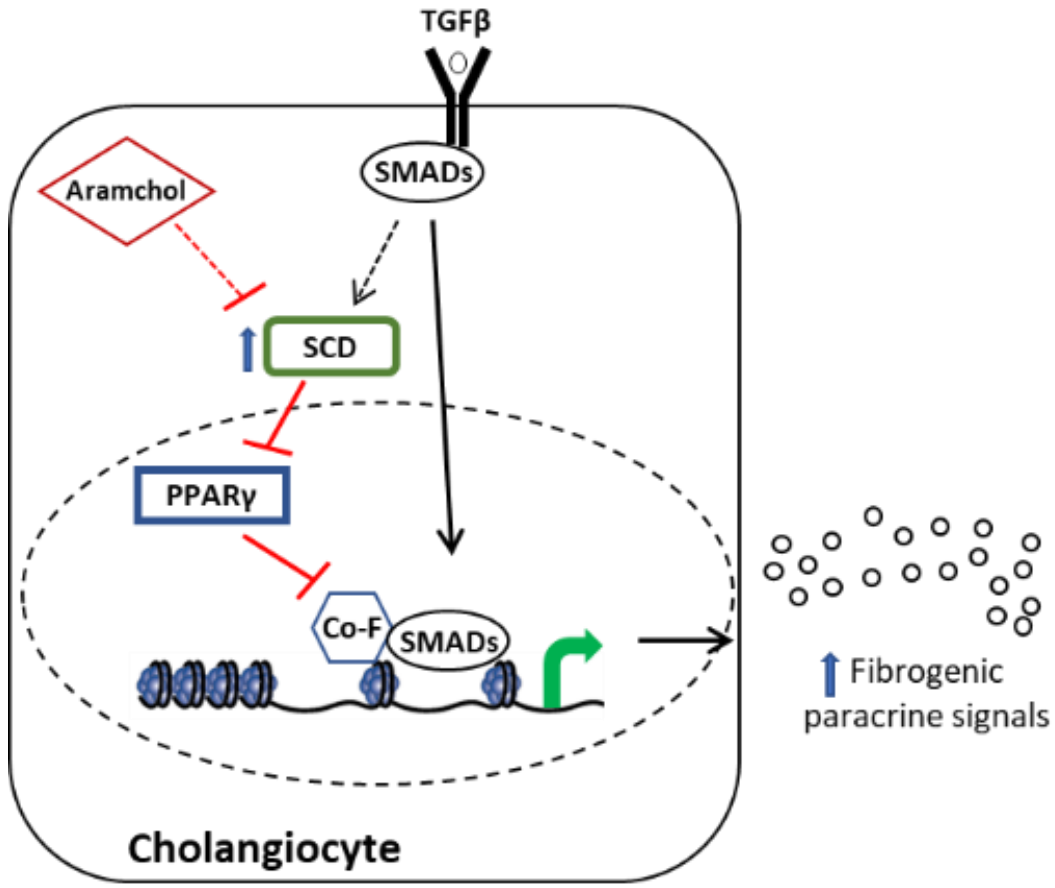
Why Aramchol for PSC?

- Primary sclerosing cholangitis (PSC) is a fibro-obliterative cholangiopathy where the disease progression is predominantly determined by biliary fibrosis
- Aramchol has been shown to downregulate SCD1, and attenuate fibrogenesis by HSCs, which may be in part due to the restoration of PPARγ and PPARγ coactivator 1α (PGC-1α) expression
- TGFβ is known to suppress PPARγ and upregulate SCD1 in some human cells, and transcriptomic landscape of TGFβ-treated cholangiocytes showed activation of fibrogenic pathways
- Aramchol may have direct effects on cholangiocytes to reduce the production of fibrogenic and inflammatory signals that activate HSCs suggesting that Aramchol may be beneficial in treating PSC



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Aramchol in PSC and Biliary Fibrosis- Phase 2a PoC Clinical Study Outline

An Open-label, Single Arm, Phase 2a Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Aramchol Meglumine in Patients with Primary Sclerosing Cholangitis

- **Study Objectives**
  - Evaluate the safety, tolerability and PK of Aramchol meglumine
  - Explore the improvements in cholestasis, biliary injury and fibrosis, and oncogenic markers following treatment with Aramchol meglumine
- **Estimated Enrollment-** Approximately 16 patients
- **Study's endpoints-** Endpoints will include safety/tolerability measures, the conventional relevant laboratory parameters (alkaline phosphatase-ALP and bilirubin), as well as sophisticated methodologies, including MR Elastography (MRE) to measure liver stiffness, MR cholangiopancreatography (MRCP) using hepatocyte-specific contrast agents to image the biliary tract, histological fibrosis and molecular assessment and a range of biomarkers to assess disease activity and fibrosis
- As most patients in the study are expected to experience IBD, and especially UC, the study will also assess the status of UC, inflammatory markers and relevant patients reported outcomes (PROs)
- **Study Initiation**- Q4 2023
- **Study Duration**- 24 weeks

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Conclusions

- Aramchol meglumine is a Ph3 compound which has a good safety profile and demonstrated robust anti fibrotic effects in the liver and in other pre-clinical fibrotic models/ indications.

- Galmed's PSC clinical plan is comprehensive with results expected in a limited & target budget which are expected to significantly accelerate the Aramchol Meglumine clinical program forward

- Aramchol Meglumine is an improved optimized version of Aramchol with NCE patent protection up to 2035 (fibrosis patent up to 2038)

- It is expected that Aramchol meglumine could treat a wide range of other fibrotic indications. Initiation of additional clinical studies is subject to the securing financing.

- Galmed has not abandoned NASH, and Phase 3 Registrational study and plans to resume the study if the FDA and market conditions allow.

Safe Harbor and Disclaimer Statement

This presentation contains forward-looking statements about our expectations, beliefs or intentions regarding, among other things, our product development efforts, business, financial condition, results of operations, strategies or prospects. In addition, from time to time, we or our representatives have made or may make forward- looking statements, orally or in writing. Forward-looking statements may include, but are not limited to, statements relating to our objectives, plans and strategies, as well as statements, other than historical facts, that address activities, events or developments that we intend, expect, project, believe or anticipate will or may occur in the future. These statements are often characterized by terminology such as “believe,” “hope,” “may,” “anticipate,” “should,” “intend,” “plan,” “will,” “expect,” “estimate,” “project,” “positioned,” “strategy” and similar expressions and are based on assumptions and assessments made in light of management’s experience and perception of historical trends, current conditions, expected future developments and other factors believed to be appropriate.

These forward-looking statements may be included in, but are not limited to, this presentation, various filings made by us with the SEC, press releases or oral statements made by or with the approval of one of our authorized executive officers. Forward-looking statements relate to anticipated or expected events, activities, trends or results as of the date they are made. Because forward-looking statements relate to matters that have not yet occurred, these statements are inherently subject to risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements. Forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statements. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements, including, but not limited to, the factors summarized below.

These factors include, but are not limited to, the following: the timing and cost of our planned PSC clinical trial and our pivotal Phase 3 ARMOR trial, or the ARMOR Study (if re-initated) or any other pre-clinical or clinical trials; completion and receiving favorable results of our planned PSC clinical trial and our the ARMOR Study for Aramchol (if re-initiated) or any other pre-clinical or clinical trial; the impact of any resurgence of the COVID-19 pandemic; regulatory action with respect to Aramchol or any other product candidate by the U.S. Food and Drug Administration or the European Medicines Agency; the commercial launch and future sales of Aramchol or any other future products or product candidates; our ability to comply with all applicable post-market regulatory requirements for Aramchol or any other product candidate in the countries in which it seeks to market the product; our ability to achieve favorable pricing for Aramchol or any other product candidate; our expectations regarding the commercial market for NASH patients or any other indication; third-party payor reimbursement for Aramchol or any other product candidate; our estimates regarding anticipated capital requirements and our needs for additional financing; market adoption of Aramchol or any other product candidate by physicians and patients; the timing, cost or other aspects of the commercial launch of Aramchol or any other product candidate; the development and approval of the use of Aramchol or any other product candidate for additional indications or in combination therapy; and our expectations regarding licensing, acquisitions and strategic operations. More detailed information about the risks and uncertainties affecting us is contained under the heading “Risk Factors” included in our most recent Annual Report on Form 20-F filed with the U.S. Securities and Exchange Commission (“SEC”) on March 29, 2023, and in other filings that we have made and may make with the SEC in the future.

These statements are only current predictions and are subject to known and unknown risks, uncertainties and other factors that may cause our or our industry’s actual results, levels of activity, performance or achievements to be materially different from those anticipated by the forward-looking statements. Given these uncertainties, you should not rely upon forward-looking statements as predictions of future events. All forward-looking statements attributable to us or persons acting on our behalf included in, but not limited to, this presentation speak only as of the date hereof and are expressly qualified in their entirety by the foregoing. We undertake no obligations to update or revise forward-looking statements to reflect events or circumstances that arise after the date made or to reflect the occurrence of unanticipated events. In evaluating forward-looking statements, you should consider these risks and uncertainties. This presentation shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of these securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction.