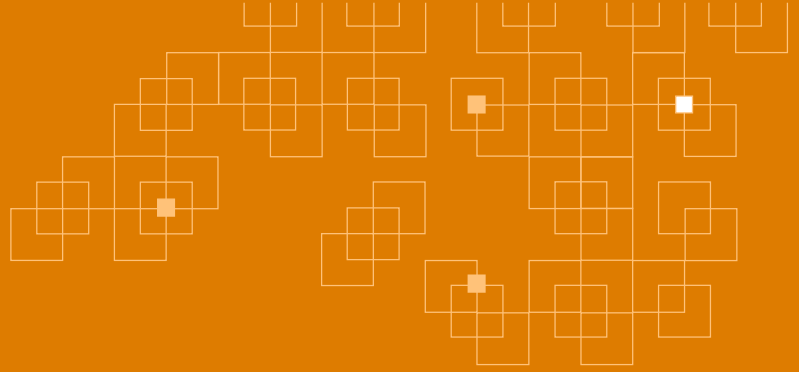

THE FORUM
For Collaborative Research℠

Landscape of Clinical Trials

Keith D. Lindor, MD

Senior Advisor to the University Provost –
Arizona State University

PSC Liver Forum – September 2019

Berkeley Public Health

PSC Clinical Trials – Closed (older)

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Study Name	Status	Recruiting	Opened Date
Ursodeoxycholic Acid	Closed	No	2009
Norursodeoxycholic Acid (NUC-3)	Closed	No	2012
A Pilot Study of Xifaxan	Closed	No	2012
Simtuzumab (GS-6624) in the Prevention of Progression of Liver Fibrosis	Closed	No	2012
Pilot Study of Fenofibrate	Closed	No	2012
Open Label Study to Evaluate Safety and Efficacy of LUM001 (CAMEO)	Closed	No	2014
Obeticholic Acid (OCA) (AESOP)	Closed	No	2014
A Trial of BTT1023 (BUTEO)	Closed	No	2014

PSC Clinical Trials - Closed

Study Name	Status	Recruiting	Opened Date
Bezafibrate	Closed	No	2015
Safety, Tolerability, and Efficacy of Cilofexor in Adults (non steriodal FXR)	Closed	No	2016
A Study Evaluating the Safety and Efficacy of Curcumin in Patients	Closed	No	2016
Phase 2 Study of NGM282 in Patients	Closed	No	2016
PERSEUS: Preliminary Efficacy and Safety of Cenicriviroc in Adult Participants	Closed	No	2016
A Research Study to Evaluate Safety and Efficacy of DUR-928	Closed	No	2018
Fecal Transplant	Closed	No	2019

PSC Clinical Trials - Open

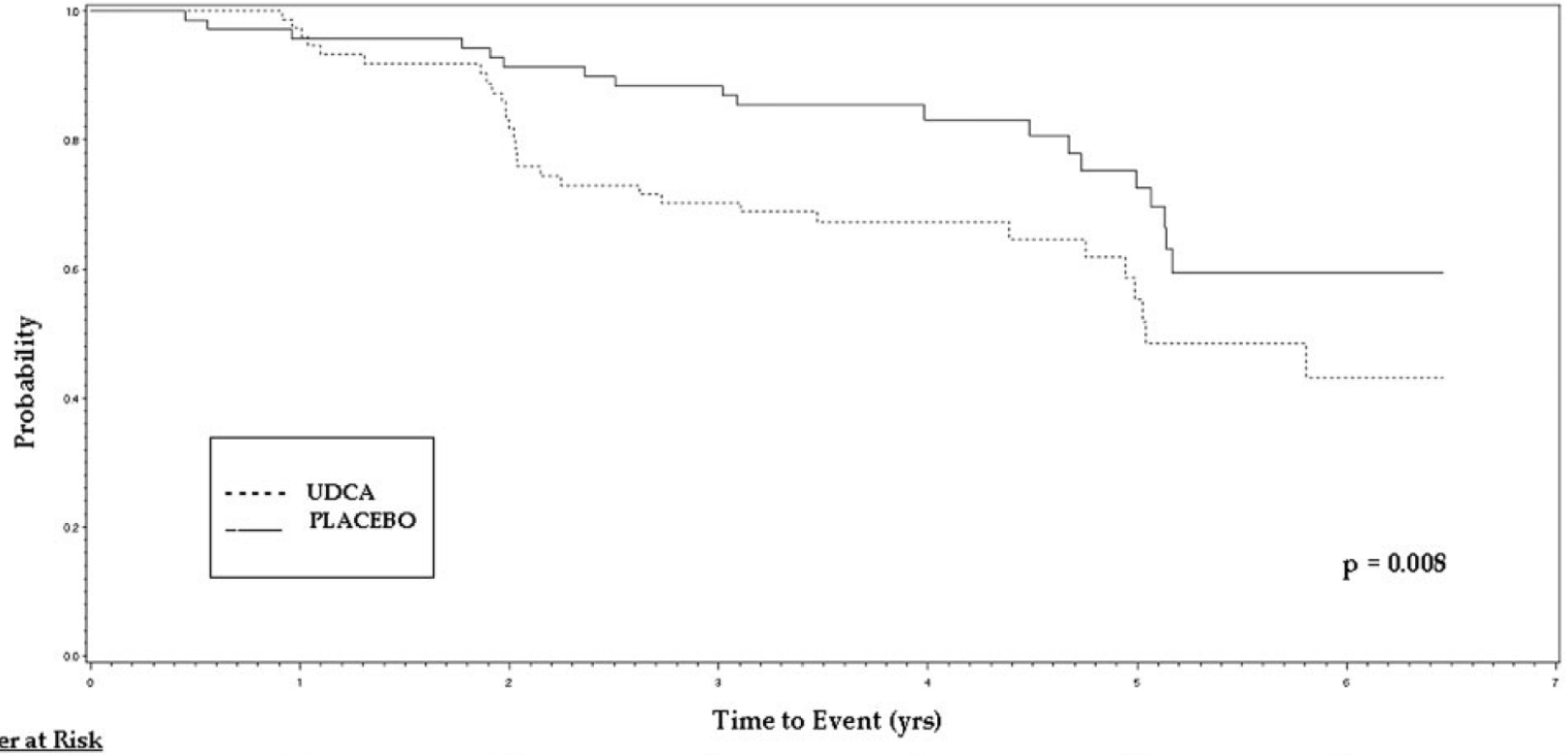
Study Name	Status	Recruiting	Opened Date
Mitomycin C Therapy for Patients	Open	Yes	2012
Vidofludimus Calcium	Open	No	2018
Vancomycin	Open	Yes	2018
Sulfasalazine (SHIP)	Open	Yes	2018
An Efficacy Trial of Low Dose All-trans Retinoic Acid	Open	Yes	2017
Dosing Ranging Study of HTD1801	Open	Yes	2018
Safety, Tolerability, and Efficacy of Cilofexor in Adults (PSC-Phase 3)	Open	Yes	2019

Studies Closed to Enrollment

Results – UDCA High Dose

Model Of All Primary Endpoints

Adjusted For Mayo Risk Score, Presence of Varices, and Stage



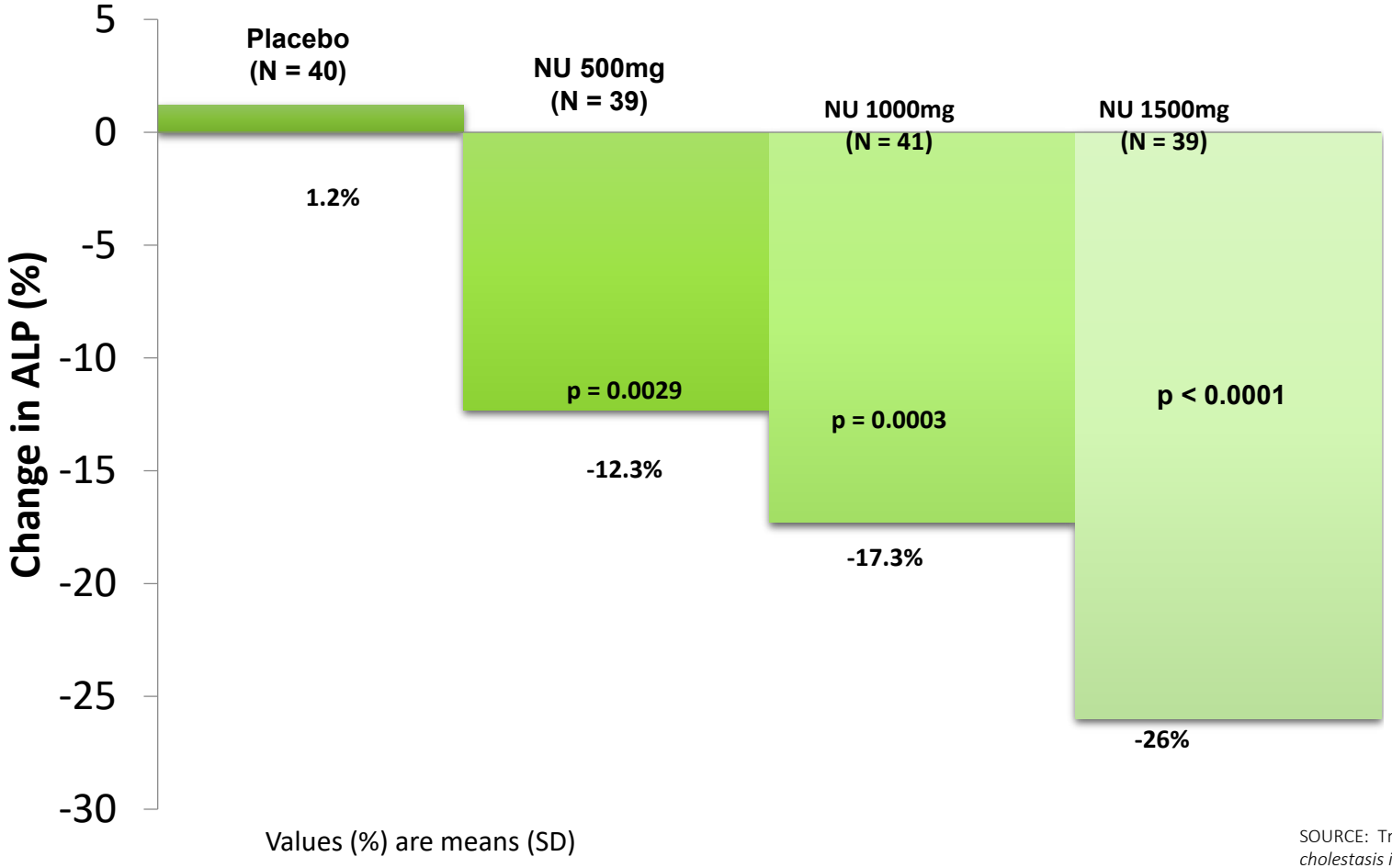
Number at Risk								
UDCA	76	73	60	51	34	18	9	0
PLACEBO	74	65	60	58	41	24	7	0

SOURCE: Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for treatment of primary sclerosing cholangitis. Hepatology 2009;50(3):808-14

Nor Ursodeoxycholic Acid

- Dr. Falk Pharma GmbH
  - Double- blind
  - 159 patients, 2 years
  - 3 doses and placebo
  - Change in alkaline phosphatase

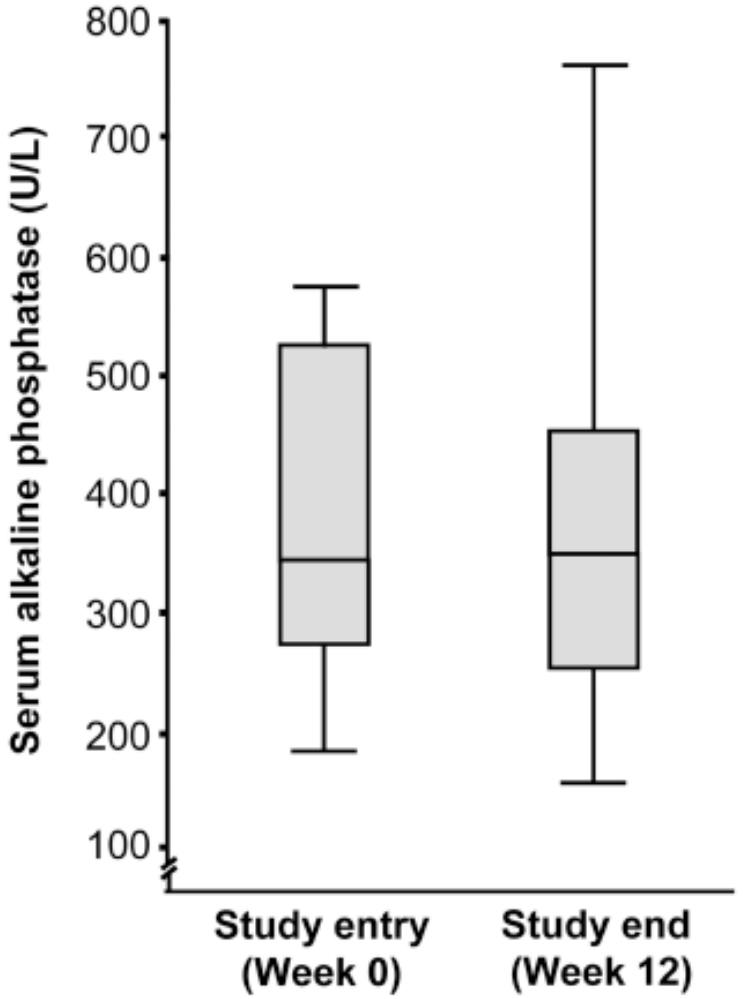
Relative Changes in ALP from Baseline to End of Treatment with nor-Urso



Values (%) are means (SD)

SOURCE: Trauner M et al. *NorUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis: results of a phase II dose finding study.* International Liver Congress, Barcelona, abstract LB02, 2016.

Serum alkaline phosphatase at baseline and after 12 weeks of rifaximin therapy - Xifaxan



Following 12 weeks of rifaximin therapy, there was no clinically or statistically significant change in the primary endpoint, serum alkaline phosphatase (p=0.47). The median serum alkaline phosphatase following 12 weeks of rifaximin therapy among individuals who completed the study (318 U/L) was also not significantly different from baseline value (i.e. per-protocol analysis, p=0.81).

SOURCE: Tabibian JH, Gossard A, El-Youssef M, et al. Prospective clinical trial of rifaximin therapy for patients with primary sclerosing cholangitis. American Journal of Therapeutics. 2017;24(1):e56-e63.

Change in Hepatic Collagen Content - Simtuzumab

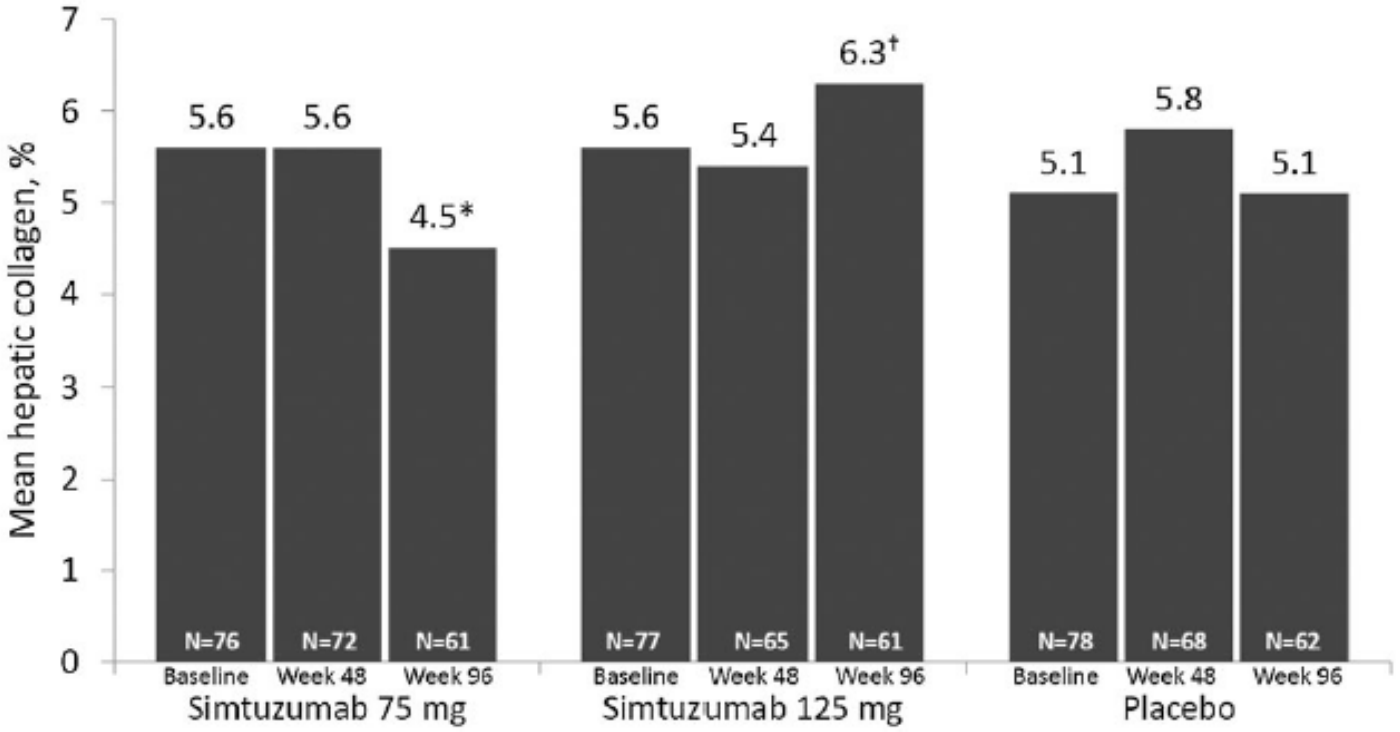
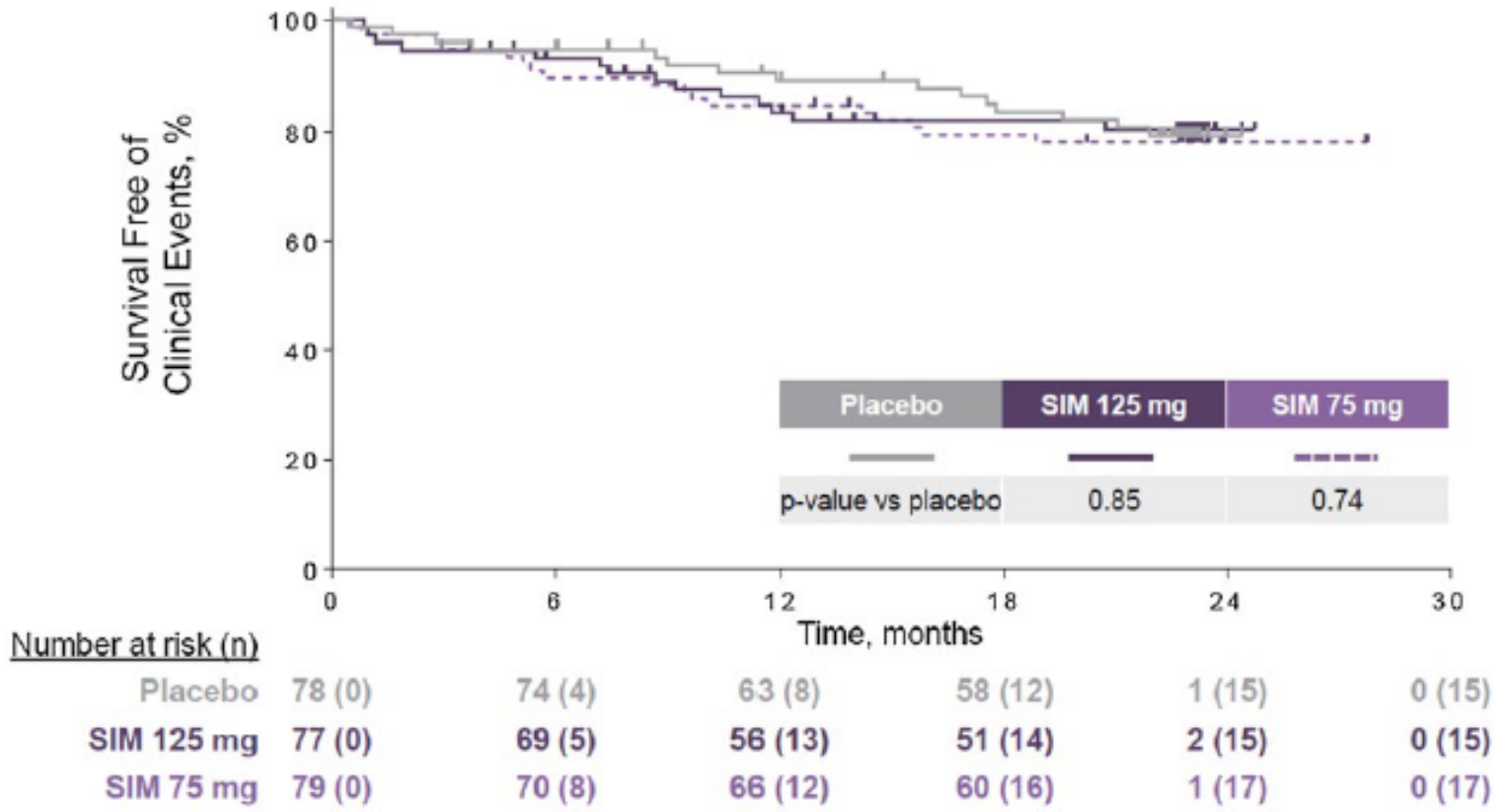


FIG. 1. Mean change in hepatic collagen content. Figure shows mean hepatic collagen content at baseline, week 48, and week 96. *P* values versus placebo are from a mixed effects model for repeated measures at week 96. *P* values are change from baseline versus placebo from a mixed-effects model. $^{*}P = 0.73$, $^{\dagger}P = 0.33$.

SOURCE: Muir AJ, Levy C, Janssen HLA, et al. Simtuzumab for PSC: Phase 2 Study Results With Insights on the Natural History of the Disease. Hepatology. 2019;69(2):684-698.

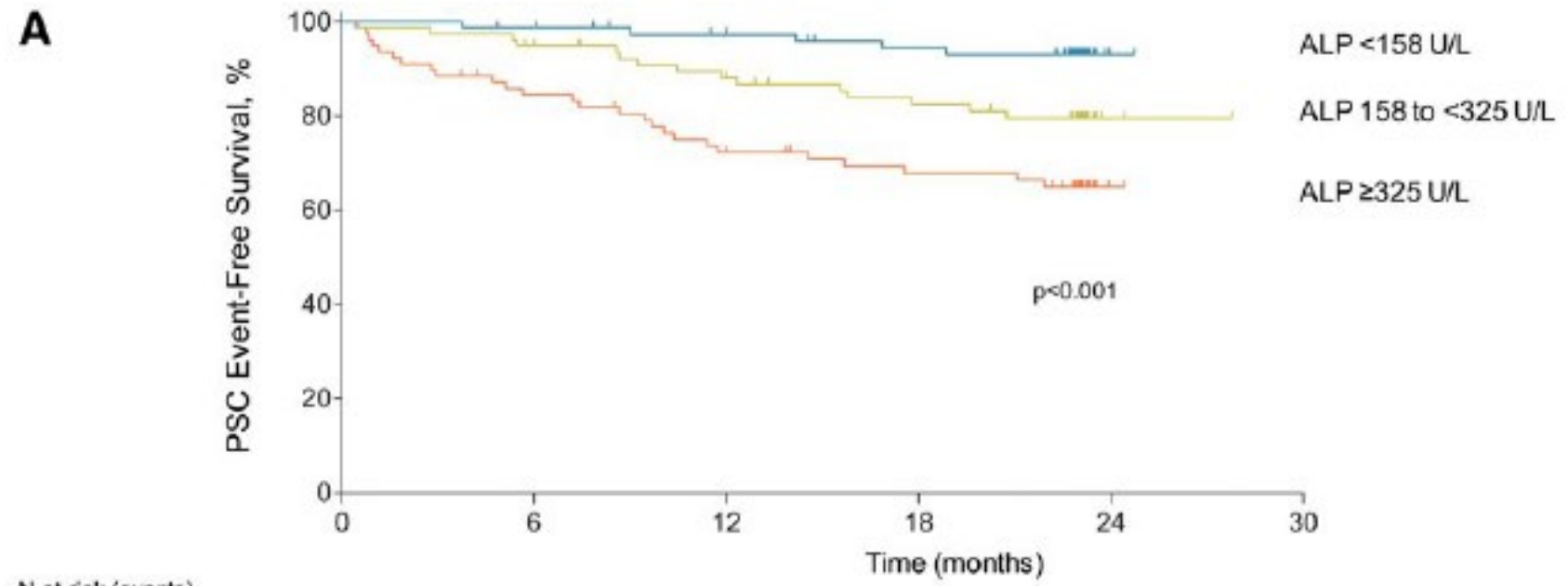
PSC Event-Free Survival by Treatment Group - Simtuzumab



SOURCE: Muir AJ, Levy C, Janssen HLA, et al. Simtuzumab for PSC: Phase 2 Study Results With Insights on the Natural History of the Disease. Hepatology. 2019;69(2):684-698.

FIG. 3. PSC event-free survival by treatment group. Figure shows survival free of PSC-related clinical events by treatment group. *P* values are by stratified log-rank test. *P* value from stratified log-rank test. Abbreviation: SIM, simtuzumab.

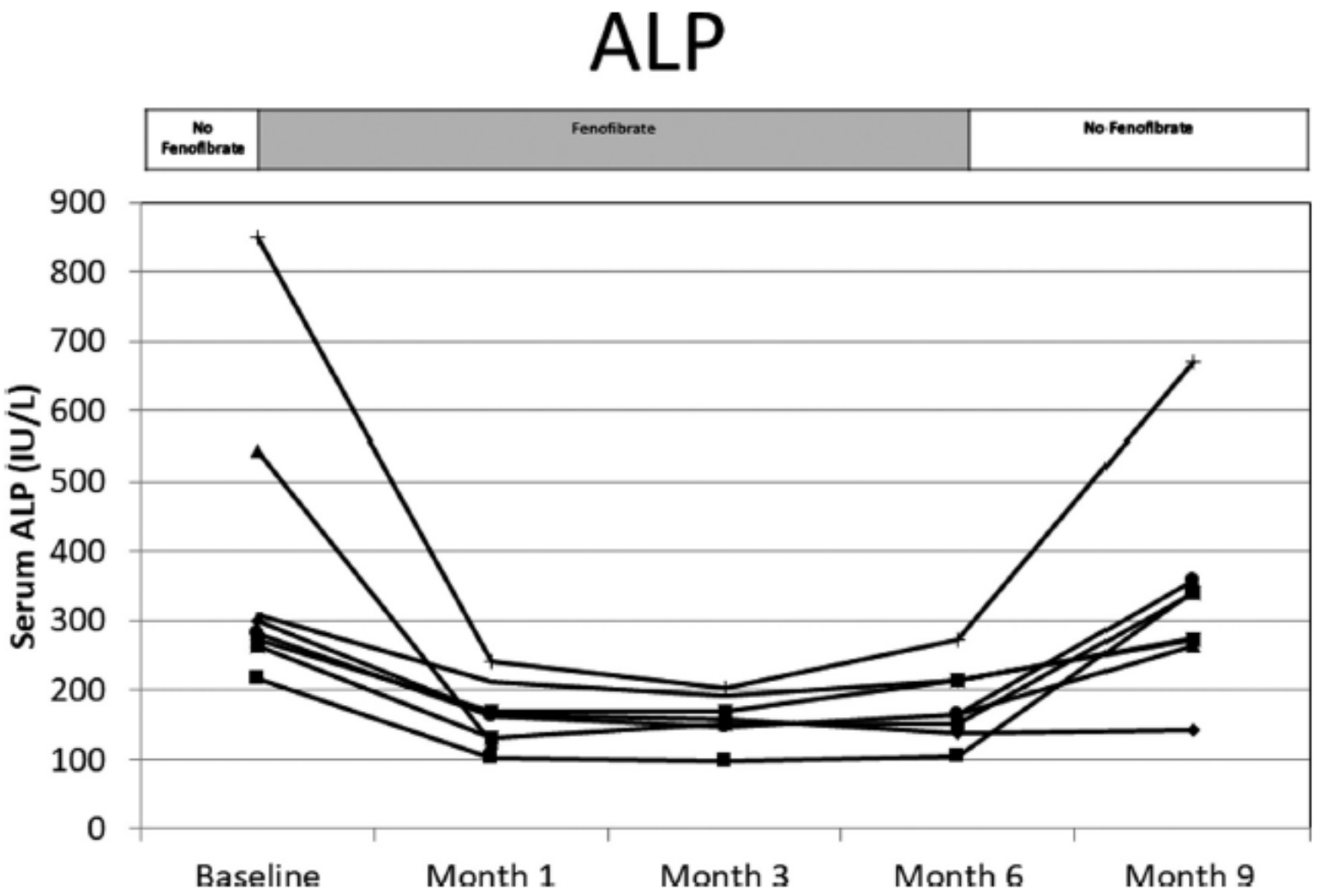
PSC Event-Free Survival by baseline ALP, baseline ELF score & change in ELF Score at week 12 - Simtuzumab



*Survival free of PSC-related clinical events by baseline ALP tertile.

Source: Muir AJ, Levy C, Janssen HLA, et al. Simtuzumab for PSC: Phase 2 Study Results With Insights on the Natural History of the Disease. Hepatology. 2019;69(2):684-698.

Trajectory of Serum Alkaline Phosphatase in PSC treated with Fenofibrate



SOURCE: Abdalla SM, Dejman A, Clark V, Levy C. Letter to the Editor: Use of Fenofibrate for patients with primary Sclerosing Cholangitis. Clinics and Research in Hepatology and Gastroenterology. (2019).

Open Label Study of Maralixibat in the Treatment of Itching in PSC

- 27 Patients
- No real change in liver tests or serum bile acid level
- No change in pruritus

Obeticholic Acid

- Intercept Pharmaceuticals

  (currently recruiting patients)

  - Multicenter
  - 75 patients, 24 weeks
  - Biochemistries, fibroscan

Obeticholic Acid for the Treatment of Patients with PSC - Results

(U/L)	Placebo (N = 25)	OCA 1.5-3 mg (N = 25)	OCA 5-10 mg (n - 26)
Mean Baseline ALP	563	423	429
Mean Change from Baseline in ALP at Week 12	-53	-57	-135*
Mean Change from Baseline in ALP at Week 24	-27	-105	-110*†
Mean Percentage from Baseline at Week 24	+1%	-22%*	-22%*

*p<0.05

† Primary endpoint was ALP change for OCA 5-10 mg compared to placebo at week 24

Use of BTT1023 (Timolumab), in the treatment of patients with PSC (BUTEO)

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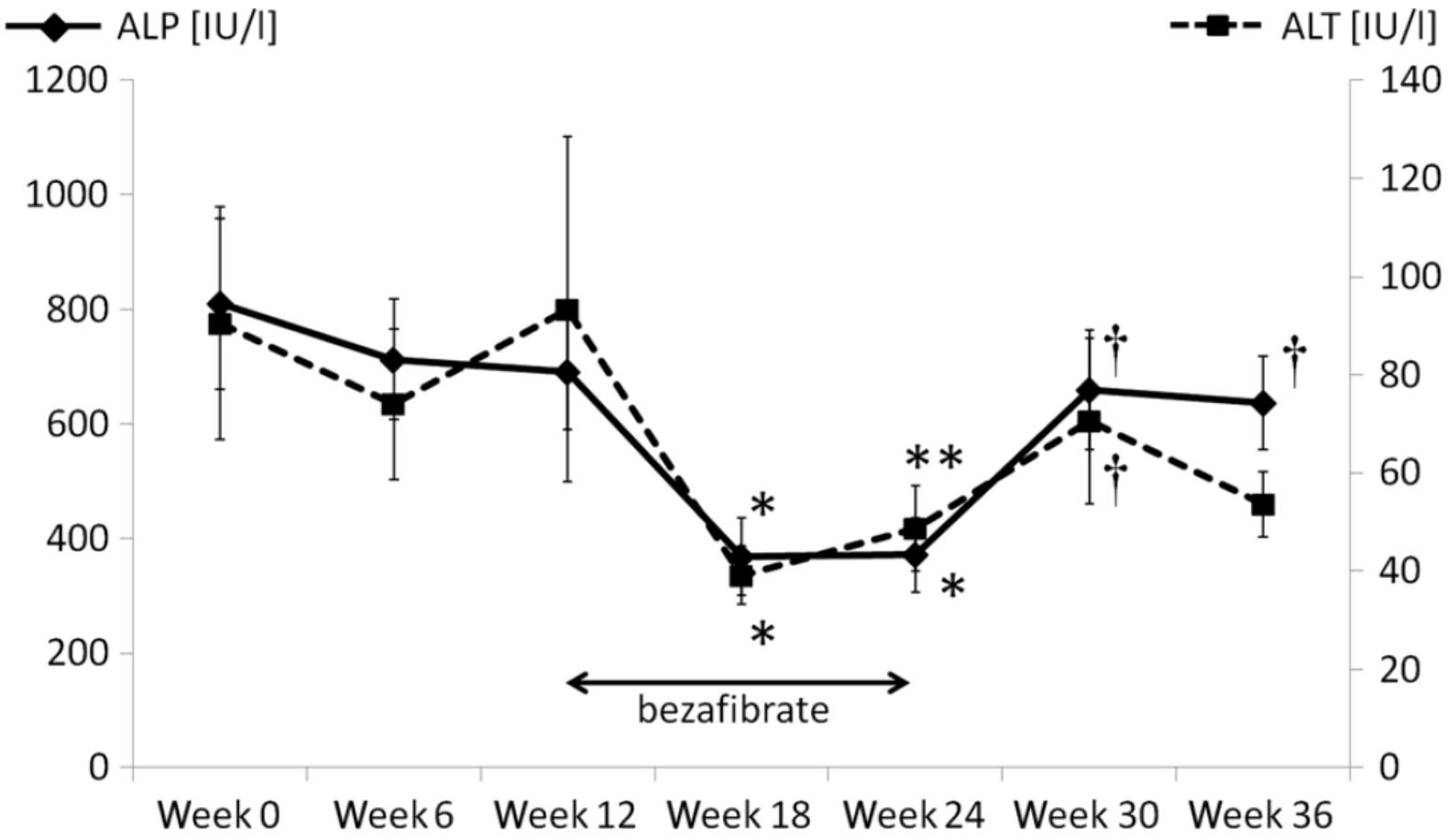
- Open label
- 59 patients
- Alkaline phosphatase improvement as endpoint
- Originally to end 2015, now closed Oct 2018

Bezafibrate

Changes in Liver Function Tests



P <0.01

** P <0.05 compared with week 12 by Wilcoxon signed-rank test

† P < 0.01 compared with week 24 by Wilcoxon signed-rank test.

Solid line indicates trend of alkaline phosphatase (ALP)

Dashed line indicates trend of alanine aminotransferase (ALT).

SOURCE: Mizuno S, Hirano K, Isayama H, et al. Prospective study of bezafibrate for the treatment of primary sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2015;22(10):766-70.

Cilofexor Improves Serum ALP in Patients with PSC

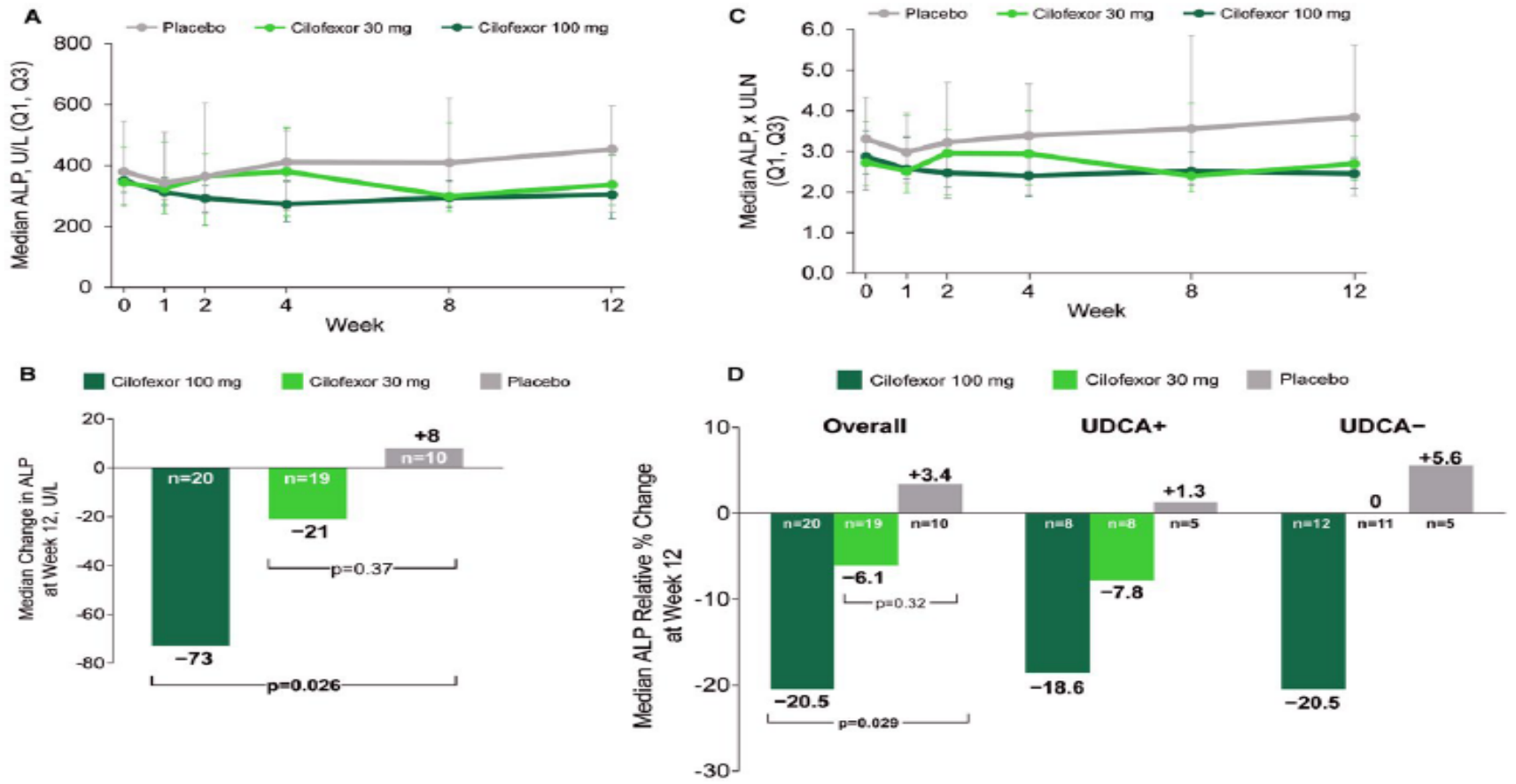
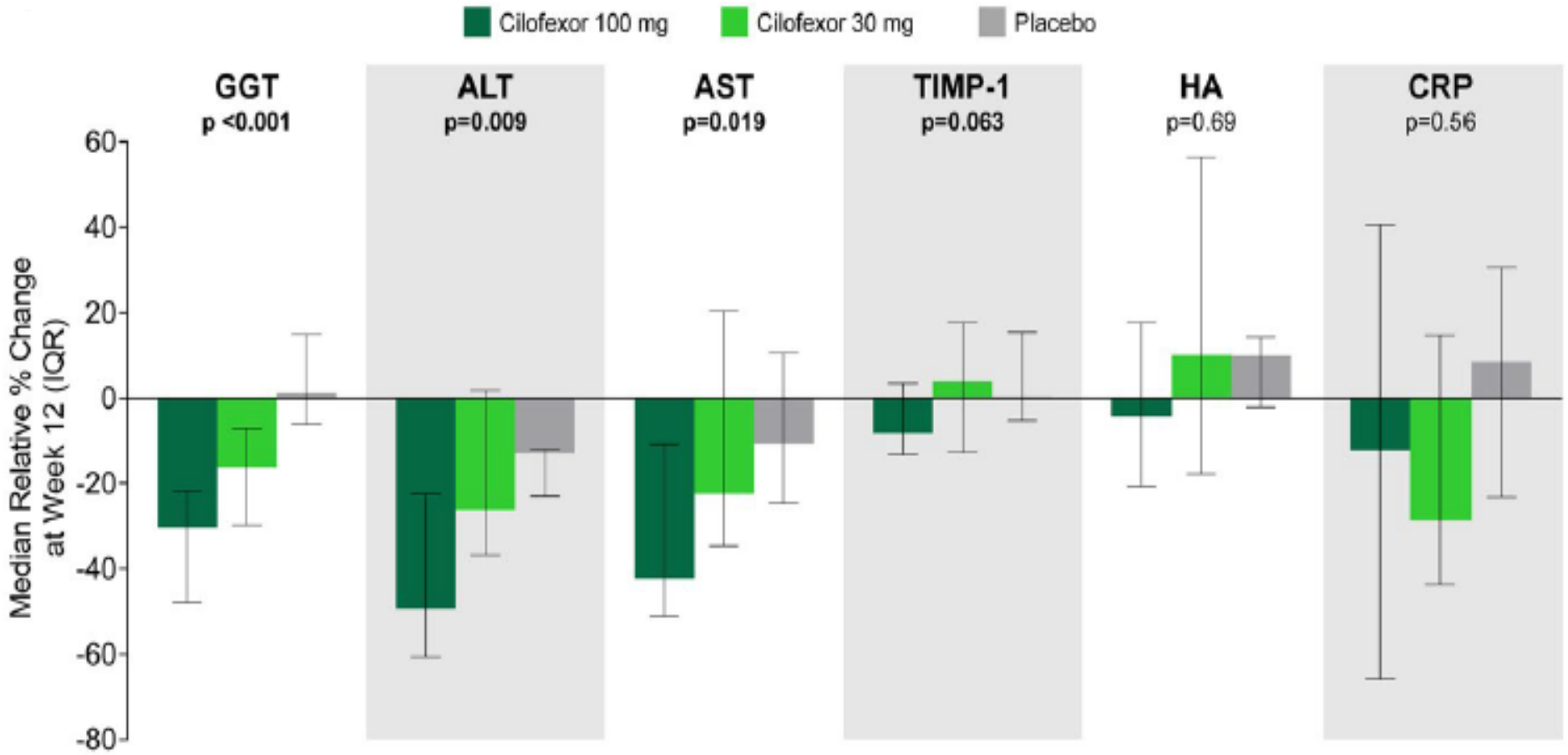


FIG. 1. Cilofexor improves serum ALP in patients with PSC. (A) Median (IQR) serum ALP between baseline and week 12 of the double-blind phase of the study. (B) Median absolute change in serum ALP from baseline to week 12 of therapy. *P* values versus placebo are according to Wilcoxon rank-sum test. (C) Median (IQR) change in serum ALP relative to the ULN between baseline and week 12 of therapy. (D) Median relative (percentage) change in serum ALP from baseline to week 12 of therapy (overall and according to UDCA treatment). *P* values versus placebo are according to Wilcoxon rank-sum test.

SOURCE: Trauner M, Gulamhusein A, Hameed B, et al. The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS-9647) Improves Markers of Cholestatis & Liver Injury in Patients with PSC. Hepatology. 2019;0(0):1-14.

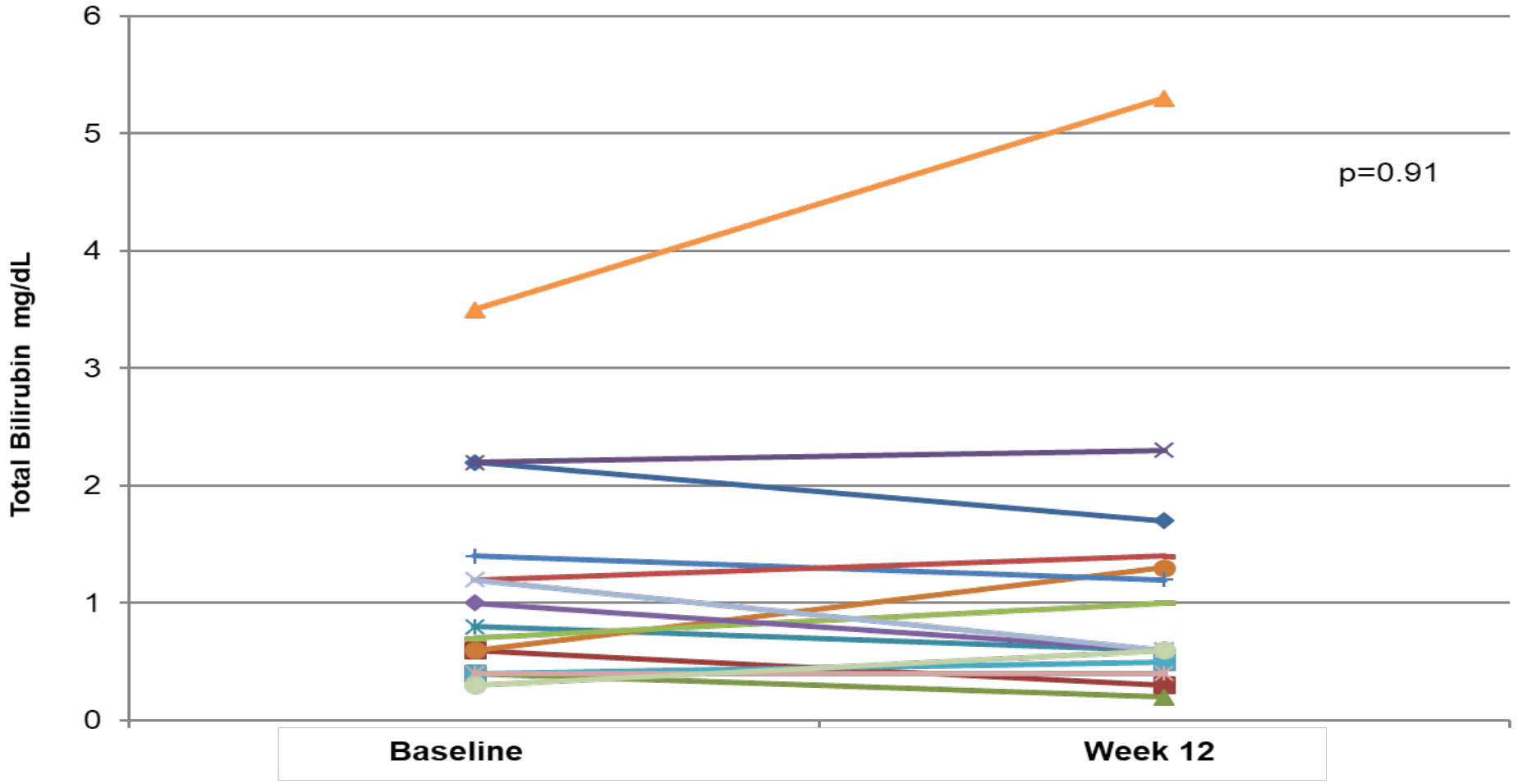
Effect of Cilofexor on Liver Biochemistry & Markers of Fibrosis & Bile Acid Homeostasis



SOURCE: Trauner M, Gulamhusein A, Hameed B, et al. The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS-9647) Improves Markers of Cholestatis & Liver Injury in Patients with PSC. Hepatology. 2019;0(0):1-14.

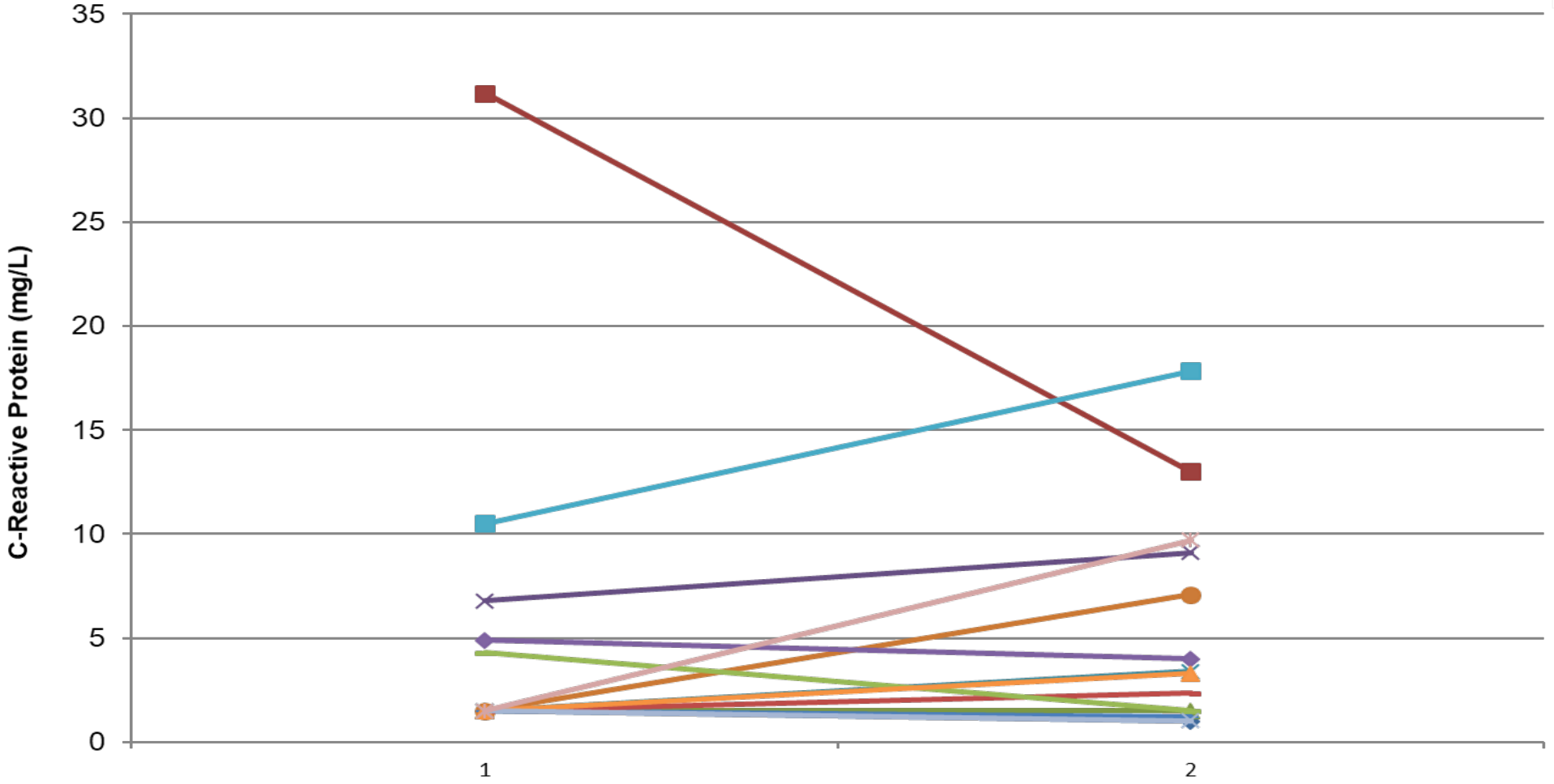
*Cilofexor 100 mg leads to improvement of serum GGt, ALT, AST & TIMP-1 compared with placebo. *P* values for cilofexor 100 mg versus placebo are according to Wilcoxon rank-sum test.

Individual Changes in Total Bilirubin Before & After Treatment - Curcumin



SOURCE: Eaton JE, Nelson KM, Gossard AA, et al. Efficacy and safety of curcumin in primary sclerosing cholangitis: an open label pilot study. Scandinavian Journal of Gastroenterology. 2019;54(5):633-639.

Individual Changes in C-Reactive Protein Before & After Treatment - Curcumin



[a] Available for 14/15 subjects

SOURCE: Eaton JE, Nelson KM, Gossard AA, et al. Efficacy and safety of curcumin in primary sclerosing cholangitis: an open label pilot study. Scandinavian Journal of Gastroenterology. 2019;54(5):633-639.

Effect of NGM282, an FGF19 analogue

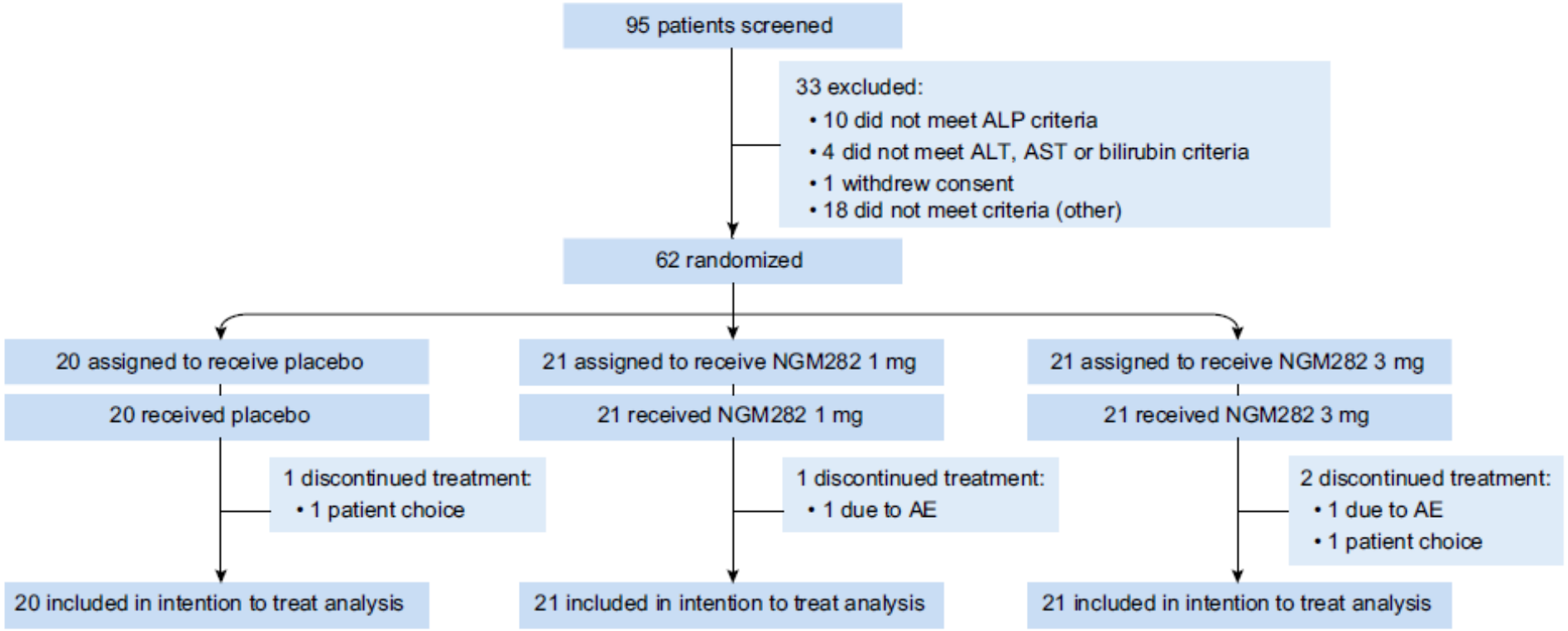


Fig. 1. Trial profile. AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

SOURCE: Hirschfield GM, Chazouilléres O, Drenth JP, et al. Effect of NGN282, an FGF19 analogue in PSC: A mulitcenter, randomized, double-blind, placebo-controlled phase II trial. Journal of Hepatology. 2019;70(3):483-493.

Effect of NGM282, an FGF19 analogue

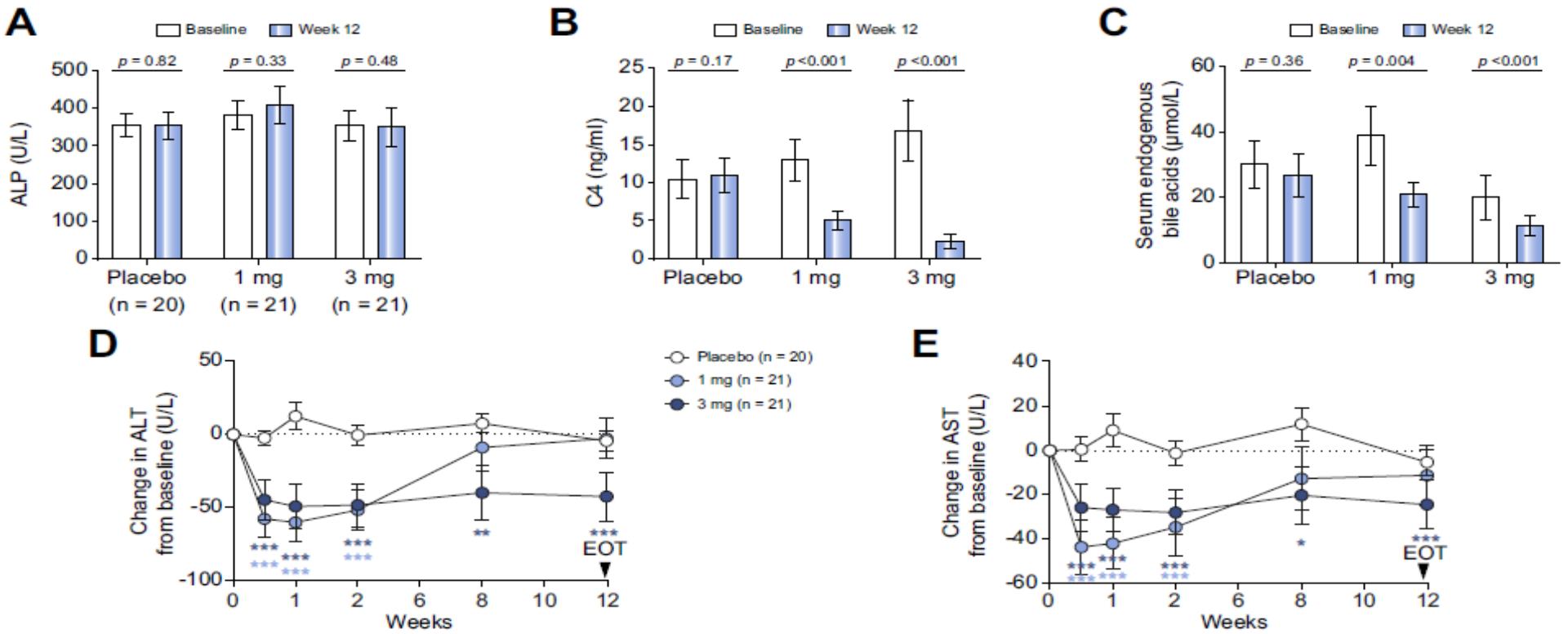
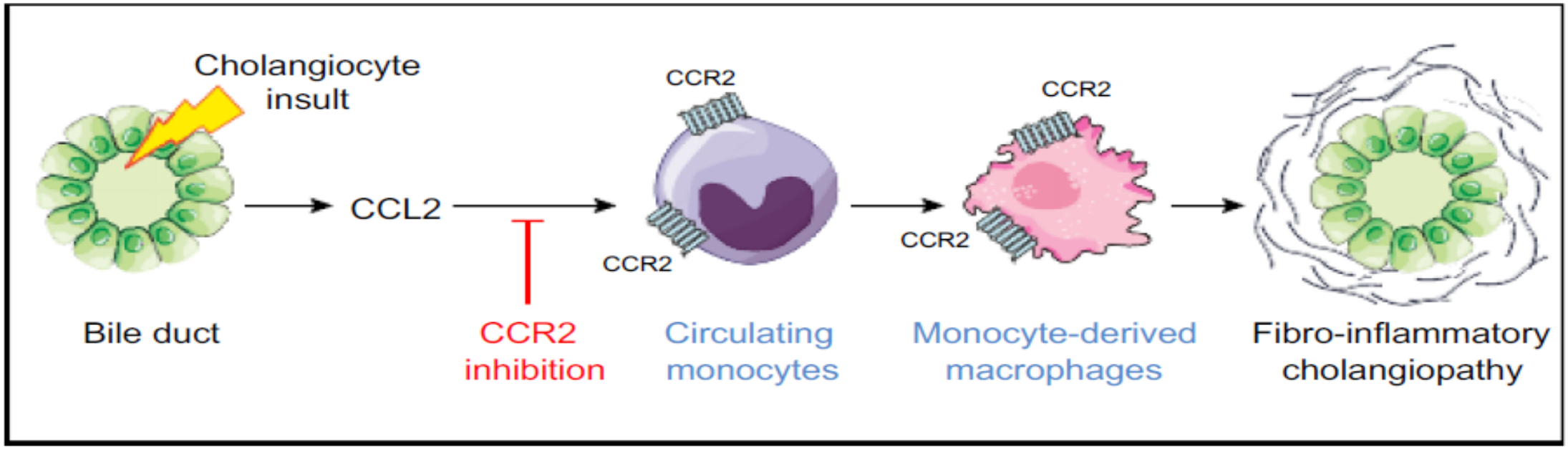


Fig. 2. Key outcome measures. (A) Serum levels of ALP at baseline and week 12. (B) Serum levels of C4 at baseline and week 12. (C) Serum levels of total endogenous bile acids at baseline and week 12. (D) Change in ALT from baseline over time. (E) Change in AST from baseline over time. All data are mean ± SEM. Statistical tests were ANCOVA (panels A-C) or mixed-effect model repeated measures (panels D-E) analyses. *p <0.05, **p <0.01, ***p <0.001. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7alpha-hydroxy-4-cholesten-3-one; EOT, end of treatment at week 12.

SOURCE: Hirschfield GM, Chazouilléres O, Drenth JP, et al. Effect of NGN282, an FGF19 analogue in PSC: A mulitcenter, randomized, double-blind, placebo-controlled phase II trial. Journal of Hepatology. 2019;70(3):483-493.

Macrophages contribute to the pathogenesis of sclerosing cholangitis in mice - Cenicriviroc



HIGHLIGHTS:

- Peribiliary macrophages are increased in PSC and animal models of PSC.
- Both M1-like and M2-like peribiliary macrophages are increased.
- Genetic & pharmacologic CCR2 inhibition restrains monocyte recruitment.
- CCR2 inhibition reduces fibrosis & cholestasis in animal models of PSC.
- These studies support the use of CCR2 inhibitors in human PSC.

SOURCE: Guicciardi ME, Trussoni CE, Krishnan A, et al. Macrophages contribute to the pathogenesis of sclerosing cholangitis in mice. Journal of Hepatology. 2018;69:676-686.

Cenicriviroc in Adult Participants with PSC

- 24 patients, is complete
- Minimal change in alkaline phosphatase (4.5% drop)
- Not published yet

Fecal Microbiota Transplant

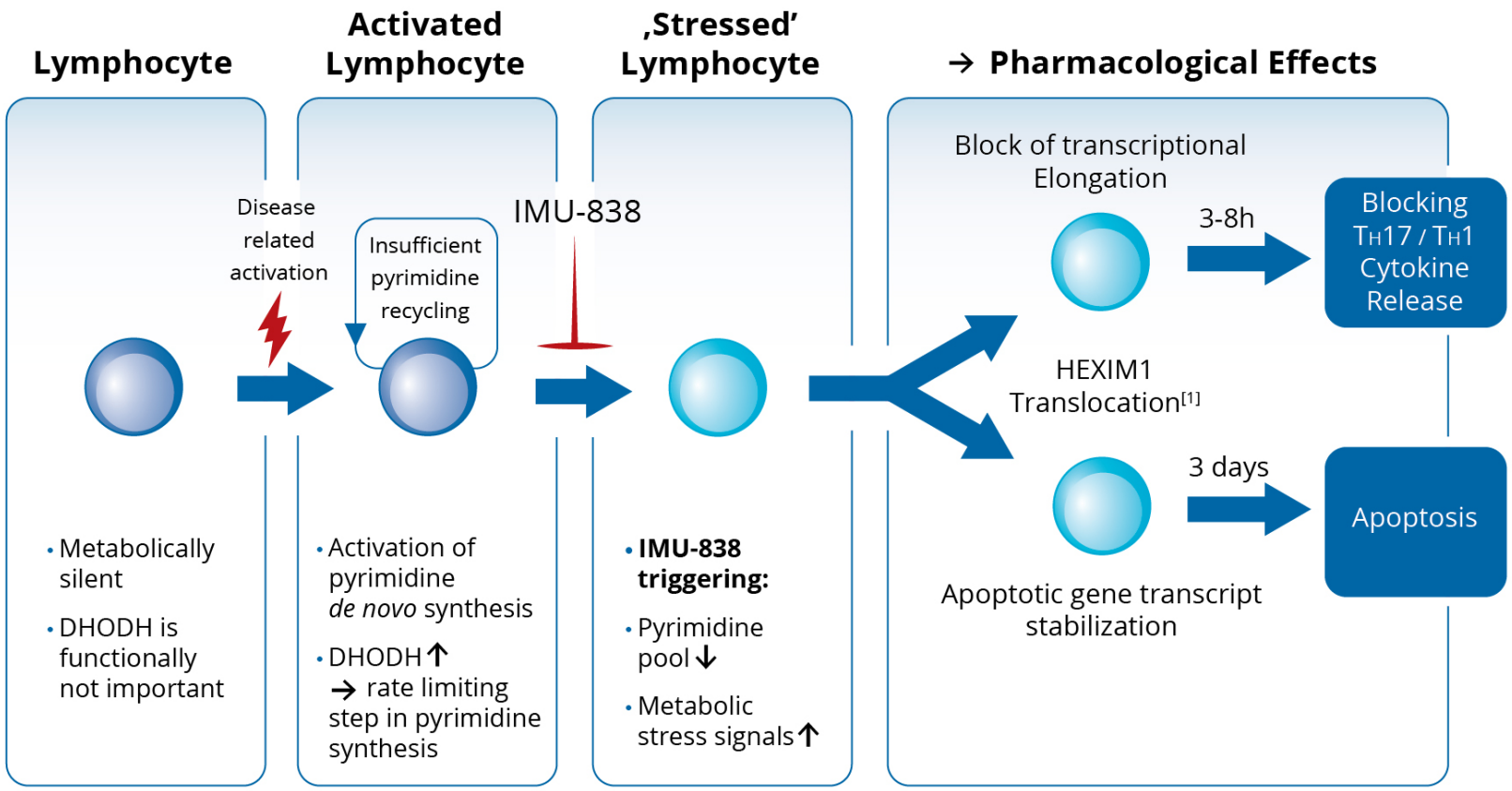
- 10 Patients, all with IBD & PSC
- 30% had ≥ 50% decrease in ALP
- Microbiome changes may correlate with ALP change

Studies Still Enrolling

Mitomycin C Therapy for Patients with PSC

- 130 patients, randomized study, 2 yrs, drug given at ERCP (up to 5x per year)
- Mayo risk score as endpoint

DHODH Inhibition Leads to Metabolic Stress in Activated Cells – Vidofludimus Calicum



[1] Tan et al., 2016, Molecular Cell 62, 34-46

SOURCE: https://www.immunic-therapeutics.com/imu-838/

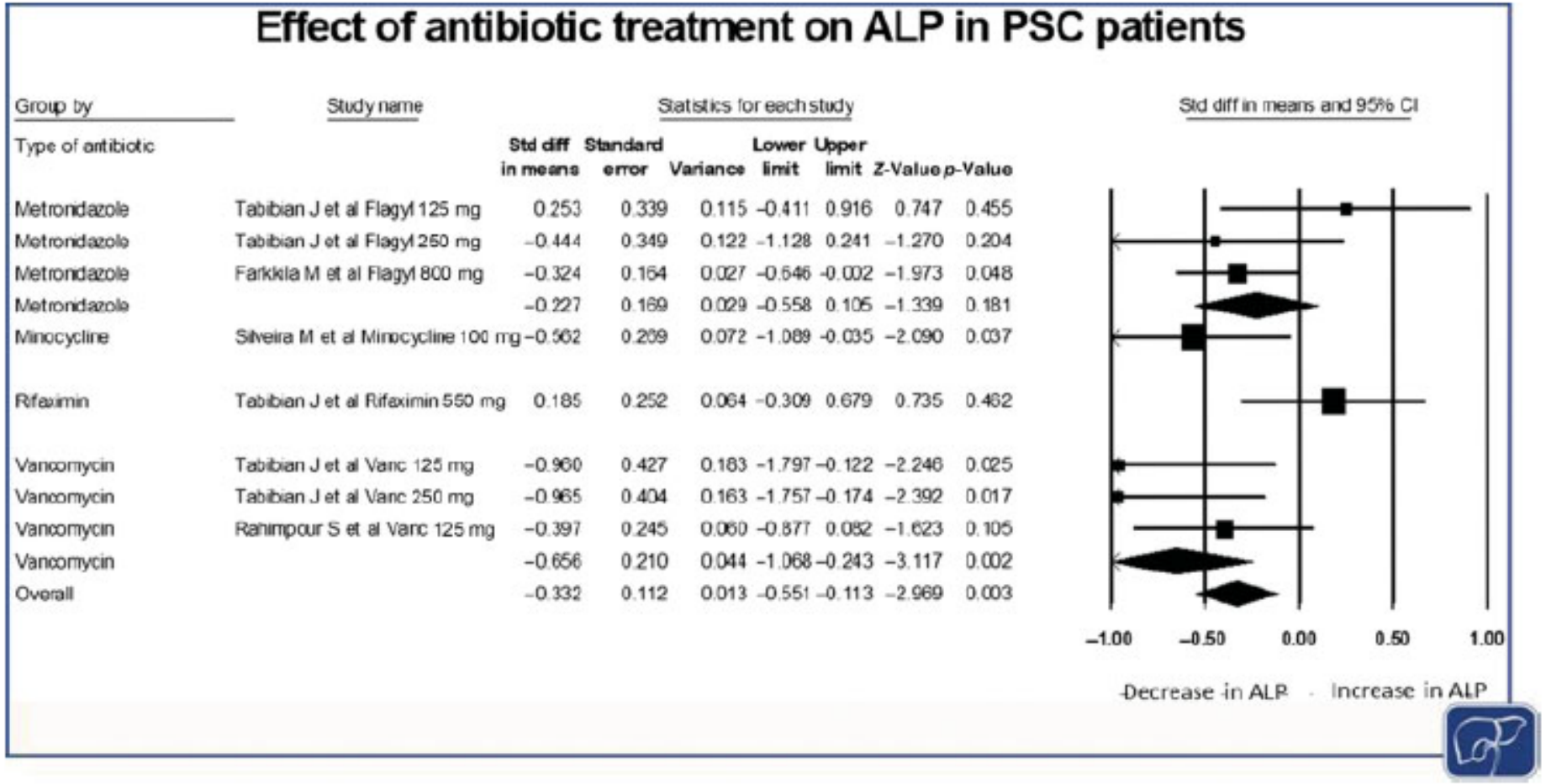
Vidofludimus Calicum

- NIH sponsored, open label
- 30 patients, 6 month treatment
- Alkaline phosphatase as endpoints

Vancomycin

- Stanford University (study is ongoing)
  - 40 patients, 3 months
  - Biochemistries, MRCP, liver tests
- Mayo Clinic (study completed)
  - 35 patients, 12 weeks
  - Biochemistries and Mayo Risk Score

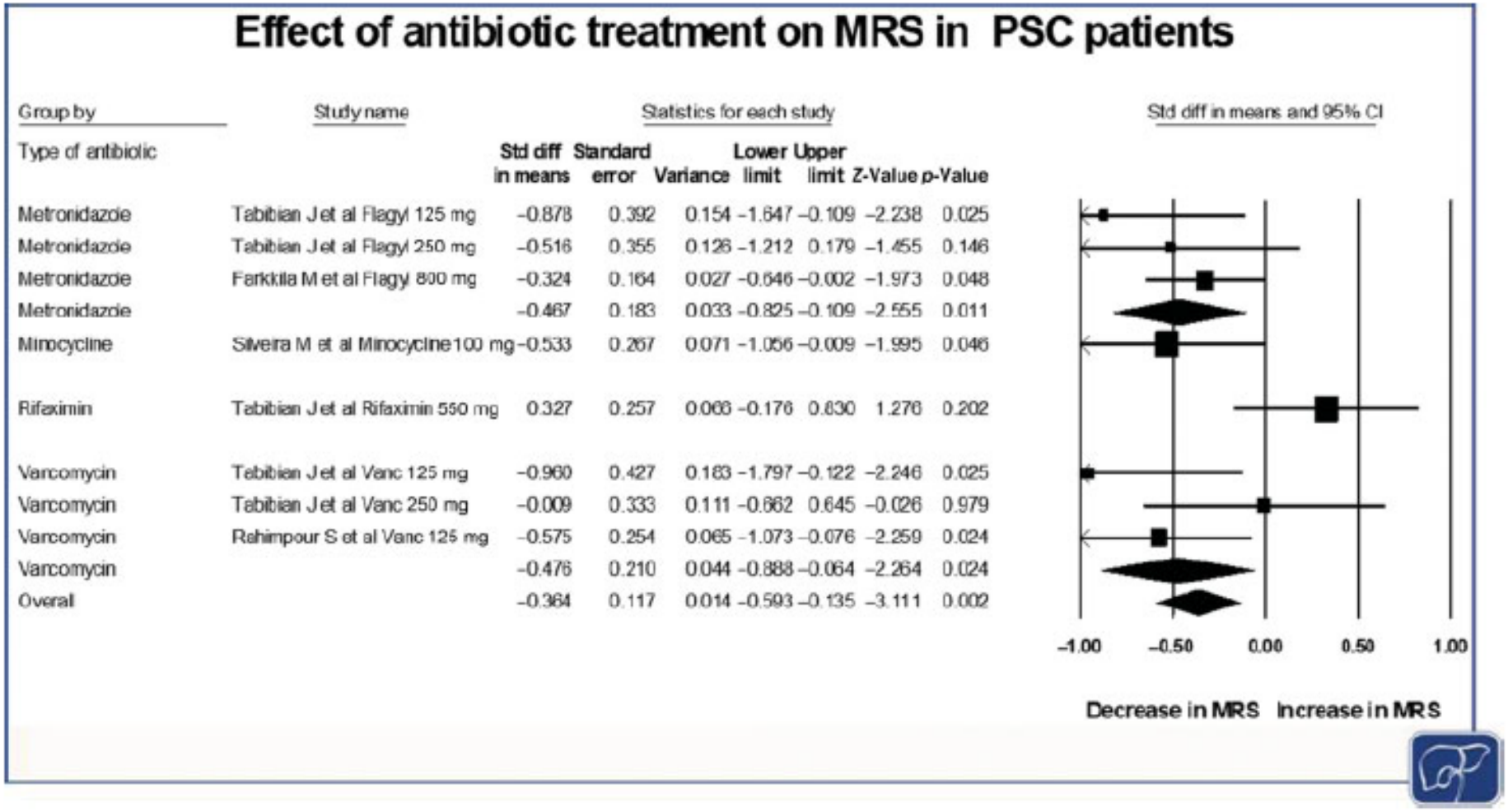
Effect of Antibiotic Treatment on ALP in PSC Patients



SOURCE: Shah A, Crawford D, Burger D, et al. Effects of Antibiotic Therapy in Primary Sclerosing Cholangitis with and without Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Seminars in Liver Disease.. 2019 Jul. doi: 10.1055/s-0039-1688501 [Epub ahead of print].

Forest plot showing the change in alkaline phosphatase (ALP) postantibiotic treatment in primary sclerosing cholangitis (PSC) patients (I_2 = 44.93, p = 0.08). CI, confidence interval.

Effect of Antibiotic Treatment on MRS in PSC Patients

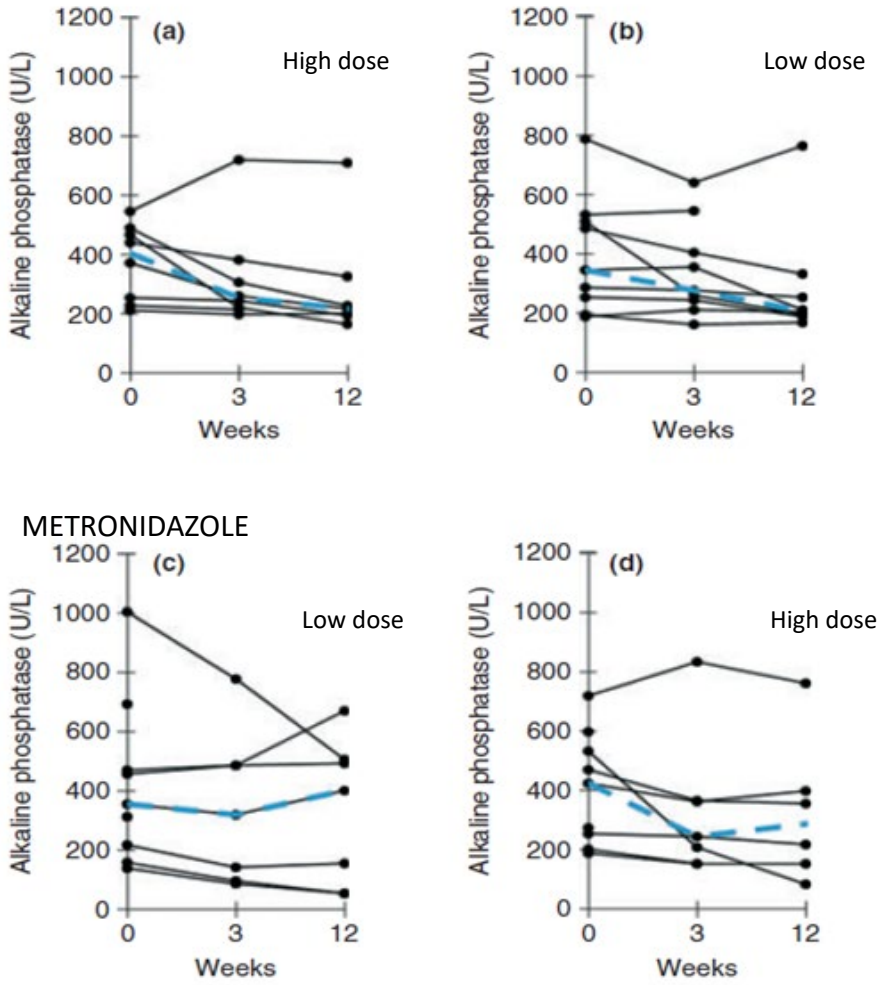


SOURCE: Shah A, Crawford D, Burger D, et al. Effects of Antibiotic Therapy in Primary Sclerosing Cholangitis with and without Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Seminars in Liver Disease.. 2019 Jul. doi: 10.1055/s-0039-1688501 [Epub ahead of print].

Forest plot showing the change in Mayo PSC risk score (MRS) postantibiotic treatment in primary sclerosing cholangitis (PSC) patients (I_2 = 47.60, p = 0.06). CI, confidence interval.

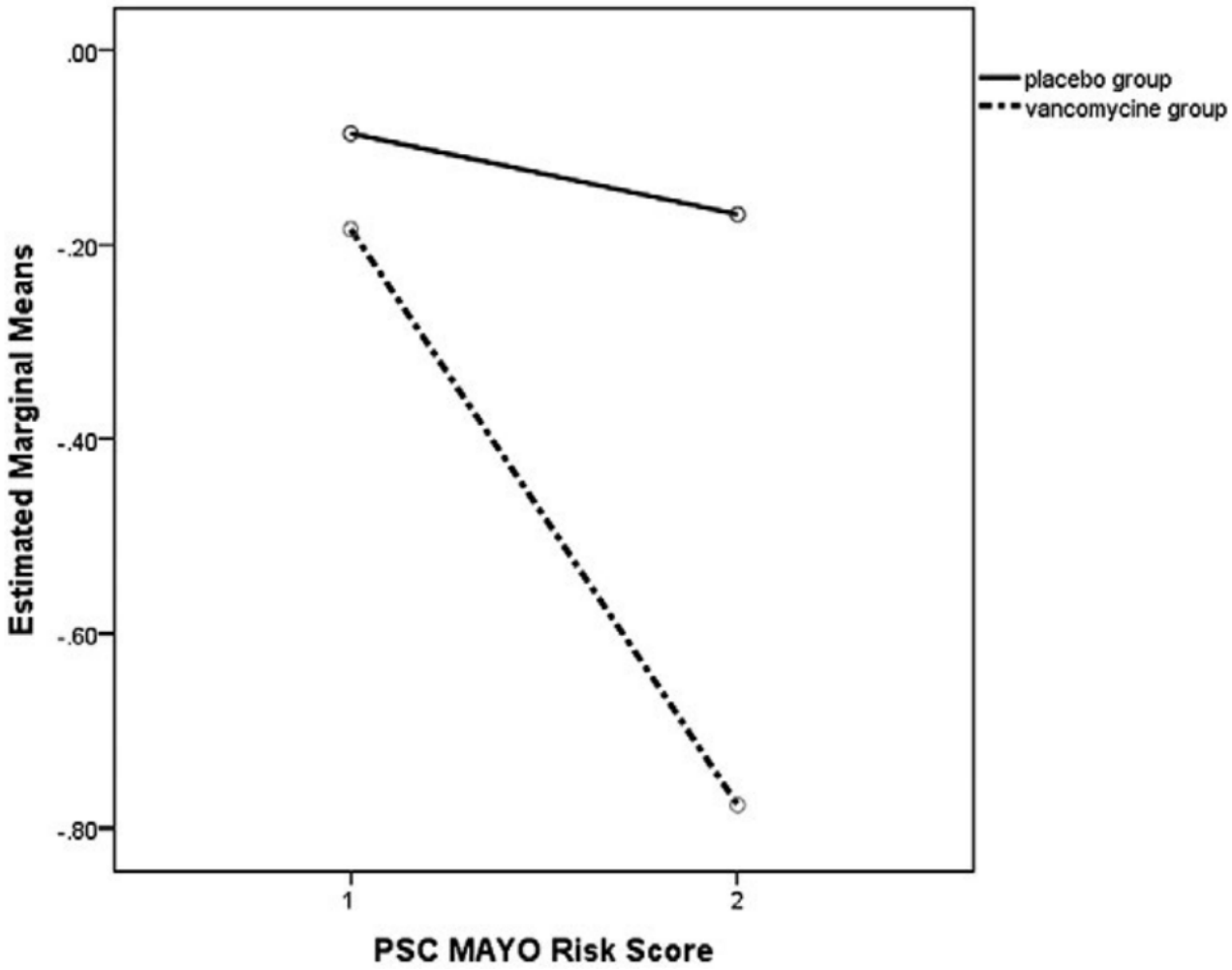
Vancomycin & Metronidazole

VANCOMYCIN



SOURCE: Tabibian JH, Weeding E, Jorgensen RA, et al. Randomized clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. Aliment Pharmacol Ther. 2013; 37(6): 604-12.

Mean Difference of PSC Mayo Risk Score in Vancomycin & Placebo Groups



SOURCE: Rahimpour S, Nasiri-toosi M, Khalili H, Ebrahimi-daryani N, Nouri-taromlou MK, Azizi Z. A Triple Blinded, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Oral Vancomycin in Primary Sclerosing Cholangitis: a Pilot Study. J Gastrointestin Liver Dis. 2016;25(4):457-464.

Sulfasalazine for the Treatment of PSC

- 42 participants, 14 weeks
- Placebo controlled, randomized
- Alkaline phosphatase endpoints
- All have IBD
- Multicenter

All-trans Retinoic Acid - PSC

- 20 patients, open label
- 6 months
- Alkaline phosphatase endpoint

Durect – PSC

- 40 patients, randomized
- 28 days
- Alkaline phosphatase endpoint
- Terminated due to poor enrollment

Hightide – Berberine – UDCA - PSC

- 90 patients
- 30 patients on each of 2 doses
- 30 patients on placebo
- 12 weeks dose finding

Mesenchymal Stem Cell - PSC

- 56 patients, open label
- IV infusion
- 2 weeks
- Alkaline phosphatase endpoint

Promising Approaches

- Nor Ursodeoxycholic Acid
- Obeticholic Acid
- Bezafibrate
- Fecal Transplant
- (NGM282)
- Vancomycin
- New Drugs in Pipeline

PSC Clinical Trials - Open

Study Name	Status	Recruiting	Opened Date
Mitomycin C Therapy for Patients	Open	Yes	2012
Vidofludimus Calcium	Open	No	2018
Vancomycin	Open	Yes	2018
Sulfasalazine (SHIP)	Open	Yes	2018
An Efficacy Trial of Low Dose All-trans Retinoic Acid	Open	Yes	2017
Dosing Ranging Study of HTD1801	Open	Yes	2018
Safety, Tolerability, and Efficacy of Cilofexor in Adults (PSC-Phase 3)	Open	Yes	2019

Conclusion

- Many drugs have been tested
- Different mechanisms
- Some studies adverse results
- Several studies actively recruiting

THANK YOU!