Lessons Learned from the Simtuzumab PSC Program

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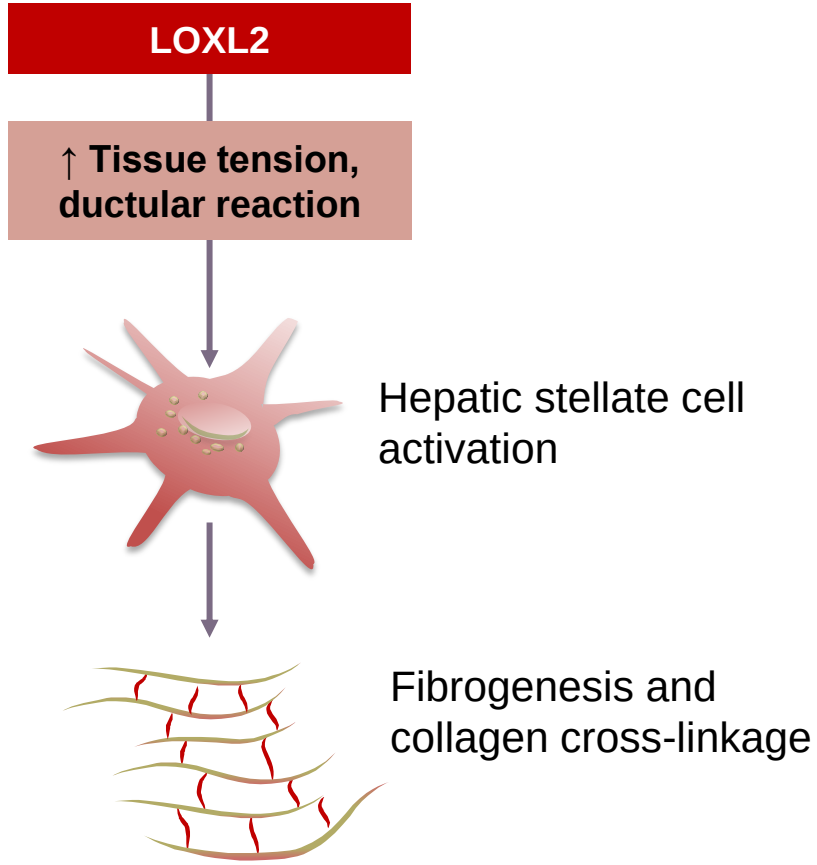
Background: Rationale for LOXL2 Inhibition in PSC

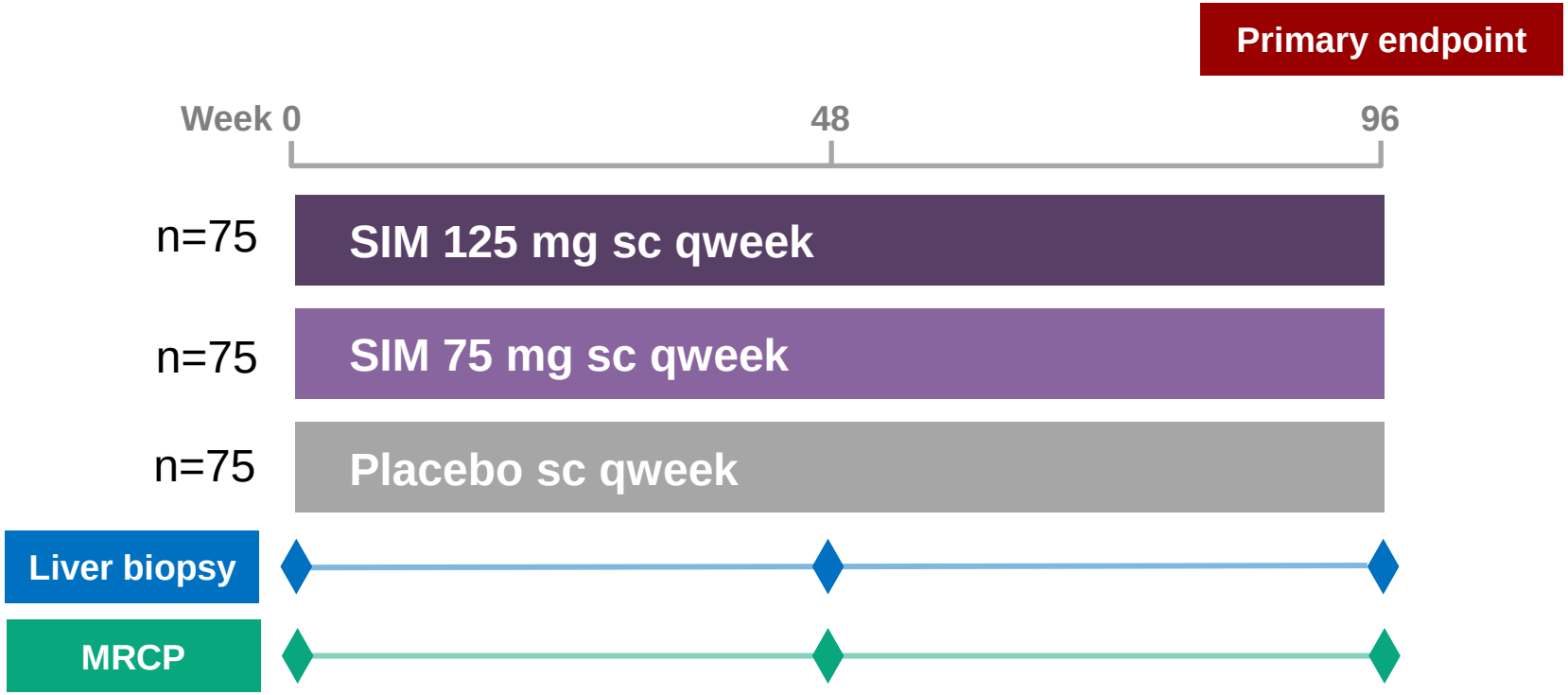
- Serum and tissue LOXL2 levels are elevated in PSC and correlate with fibrosis stage
- In pre-clinical models (e.g. MDR2 knock-out mice), LOXL2 inhibition improves fibrosis
- Simtuzumab (SIM) is a humanized IgG4 monoclonal antibody directed against LOXL2

- **Aim:** to evaluate the safety and efficacy of SIM in patients with PSC



LOXL2, lysyl-oxidase-like 2.
Barry-Hamilton V, et al. Nat Med 2010;16:1009-18; Ikenaga N, et al. AASLD 2015 (#1379);
Harrison S, et al. AASLD 2015 (#1435); French D, et al. AASLD 2016 (#378); Muir AJ, et al. EASL 2017 (Oral #PS-132).

Study Design



- Key inclusion criteria
  - Compensated PSC, confirmed on biopsy and MRCP
  - Inactive IBD (partial Mayo score ≤2; no corticosteroids or anti-TNF-α therapy)
- 1:1:1 randomization stratified by baseline serum IgG4 (> or ≤140 mg/dL)

IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; TNF-α, tumor necrosis factor-α.

Key Study Endpoints and Assessments

Safety	Adverse events, laboratory abnormalities	
Efficacy	Primary	• Morphometry for hepatic collagen
	Exploratory	• Ishak fibrosis stage • Progression to cirrhosis
	PSC-related clinical events	• Ascites, SBP • Encephalopathy, variceal hemorrhage • Ascending cholangitis, sepsis • Cholangiocarcinoma, HCC • Jaundice • Liver transplantation • Death

HCC, hepatocellular carcinoma; SBP, spontaneous bacterial peritonitis.

Results: Demographics & Baseline Characteristics

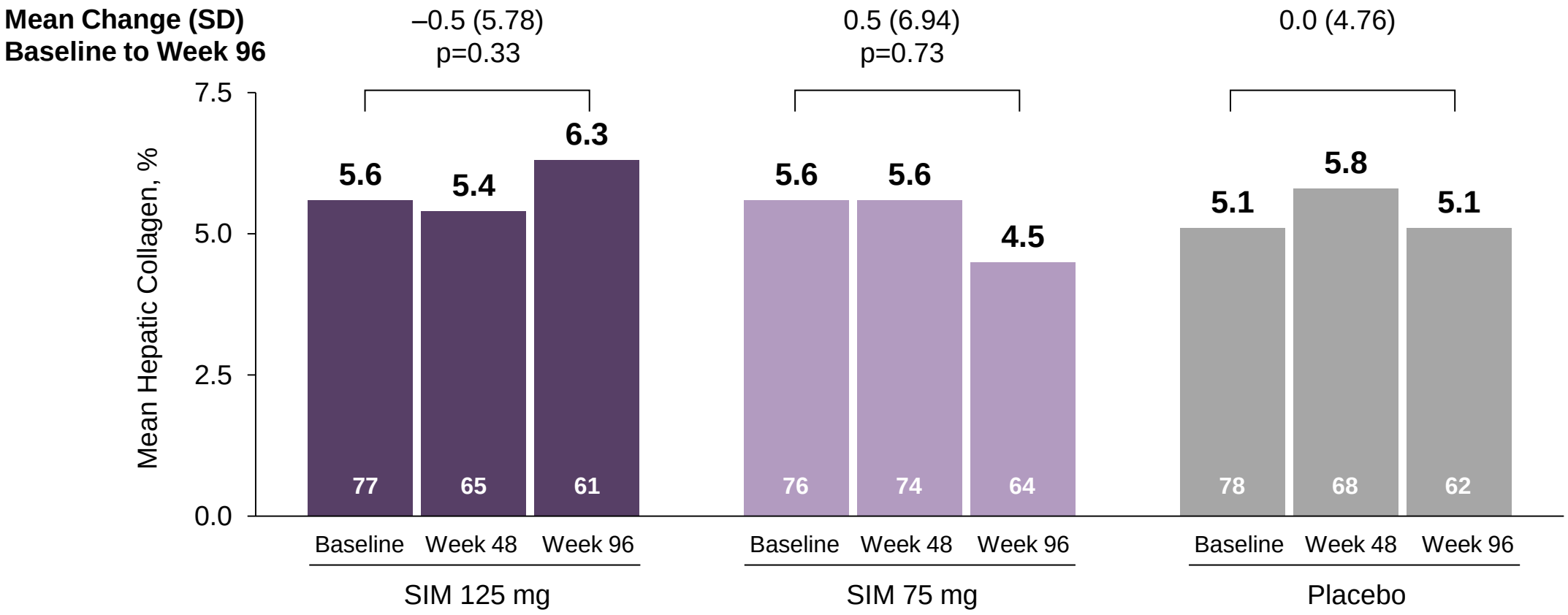
	SIM 125 mg n=77	SIM 75 mg n=79	Placebo n=78
Age, y	42 (36, 51)	45 (38, 54)	47 (35, 53)
Male, n (%)	52 (68)	52 (66)	45 (58)
Ulcerative colitis, n (%)	37 (48)	33 (42)	42 (54)
UDCA therapy, n (%)	50 (65)	42 (53)	52 (67)
sLOXL2, pg/mL	105 (71, 157)	96 (76, 146)	98 (68, 137)
ALP, U/L	271 (151, 474)	273 (134, 392)	237 (119, 336)
Bilirubin, mg/dL	0.7 (0.5, 1.2)	0.6 (0.5, 0.9)	0.7 (0.5, 1.1)
sIgG4 >140 mg/dL, n (%)	11 (14)	12 (15)	11 (14)
Ishak F3–F6, n (%)	44 (57)	40 (51)	35 (45)
Intra- and extra-hepatic disease on MRCP, n (%)	61 (79)	58 (73)	59 (76)

Continuous data are median (interquartile range [IQR]).
ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid.

Results: Study Disposition

Patients, n (%)	SIM 125 mg n=77	SIM 75 mg n=79	Placebo n=78
Completed study treatment	60 (78)	69 (87)	65 (83)
Discontinuation of study	17 (22)	10 (13)	13 (17)
Adverse event	6 (8)	4 (5)	8 (10)
Withdrew consent	5 (6)	5 (6)	5 (6)
Lost to follow-up	1 (1)	0	0

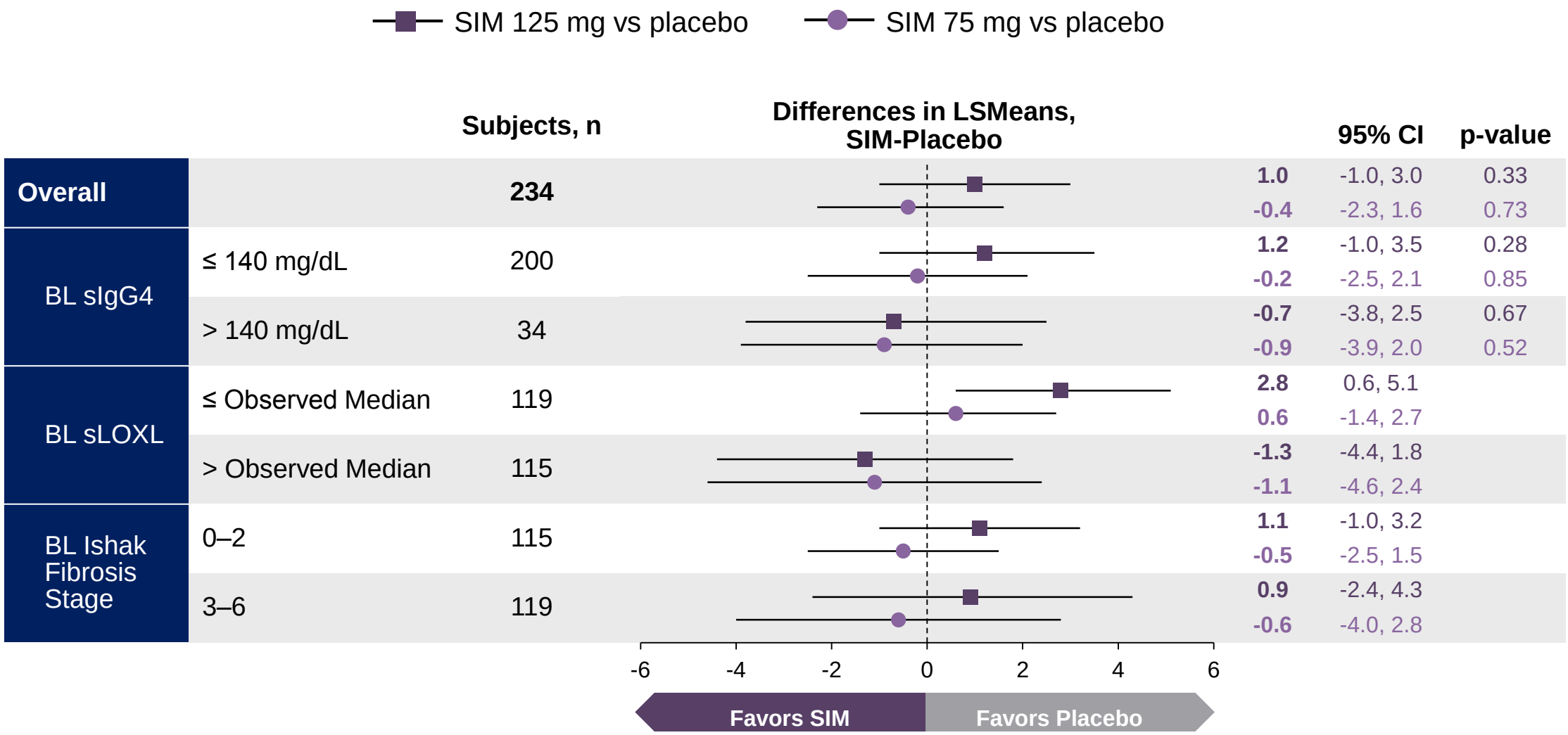
Results: No Effect of SIM on Hepatic Collagen Content



- SIM had no effect on hepatic collagen content (or α-SMA expression)

p-values vs placebo are from a mixed effect model for repeated measures at Week 96.

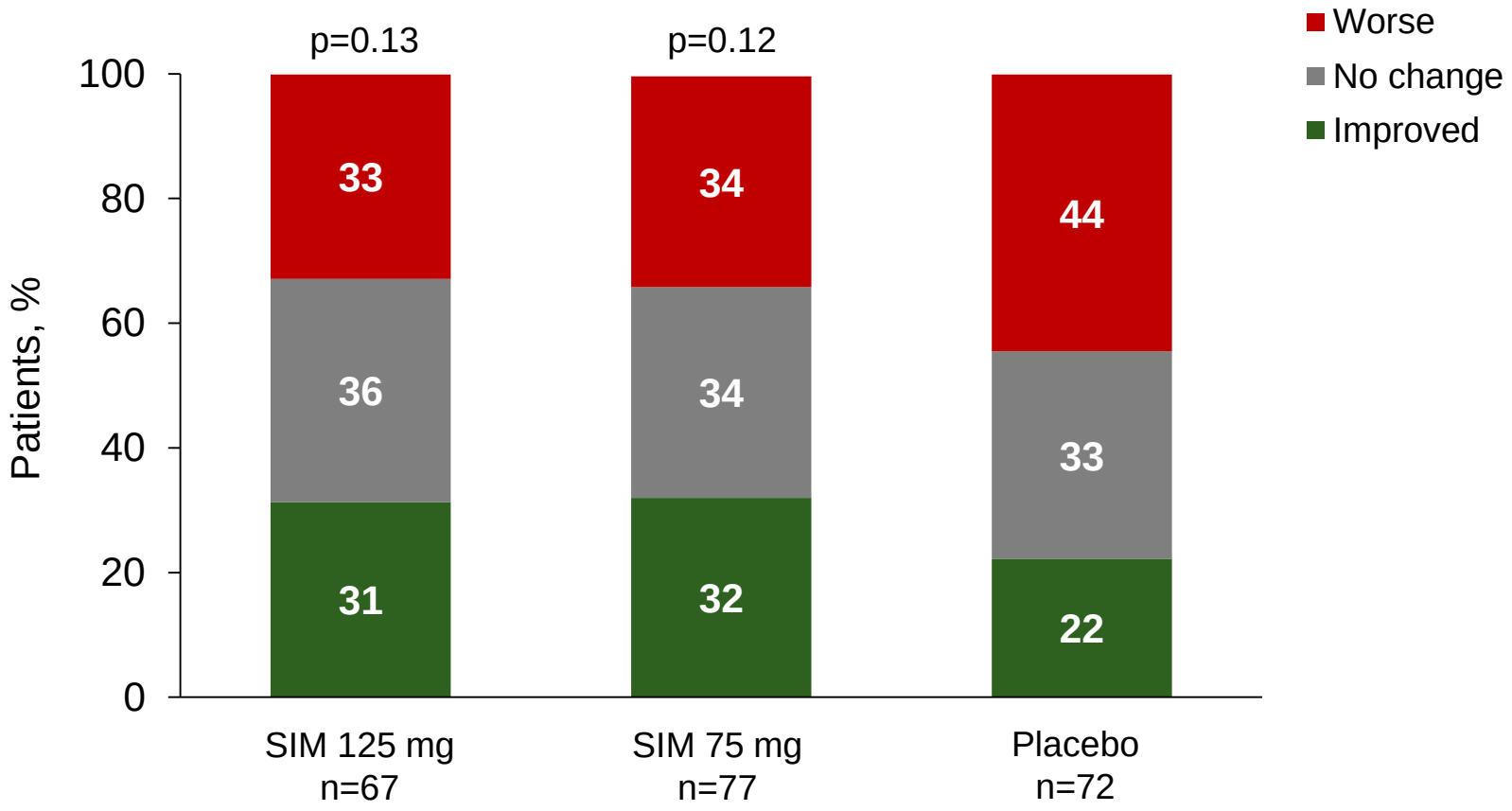
Results: Subgroup Analyses of Hepatic Collagen Content



		Subjects, n	Differences in LSMeans, SIM-Placebo	95% CI	p-value
Overall		**234**	**1.0**	-1.0, 3.0	0.33
			-0.4	-2.3, 1.6	0.73
BL sIgG4	≤ 140 mg/dL	200	**1.2**	-1.0, 3.5	0.28
			-0.2	-2.5, 2.1	0.85
	> 140 mg/dL	34	**-0.7**	-3.8, 2.5	0.67
			-0.9	-3.9, 2.0	0.52
BL sLOXL	≤ Observed Median	119	**2.8**	0.6, 5.1	
			0.6	-1.4, 2.7	
	> Observed Median	115	**-1.3**	-4.4, 1.8	
			-1.1	-4.6, 2.4	
BL Ishak Fibrosis Stage	0–2	115	**1.1**	-1.0, 3.2	
			-0.5	-2.5, 1.5	
	3–6	119	**0.9**	-2.4, 4.3	
			-0.6	-4.0, 2.8	

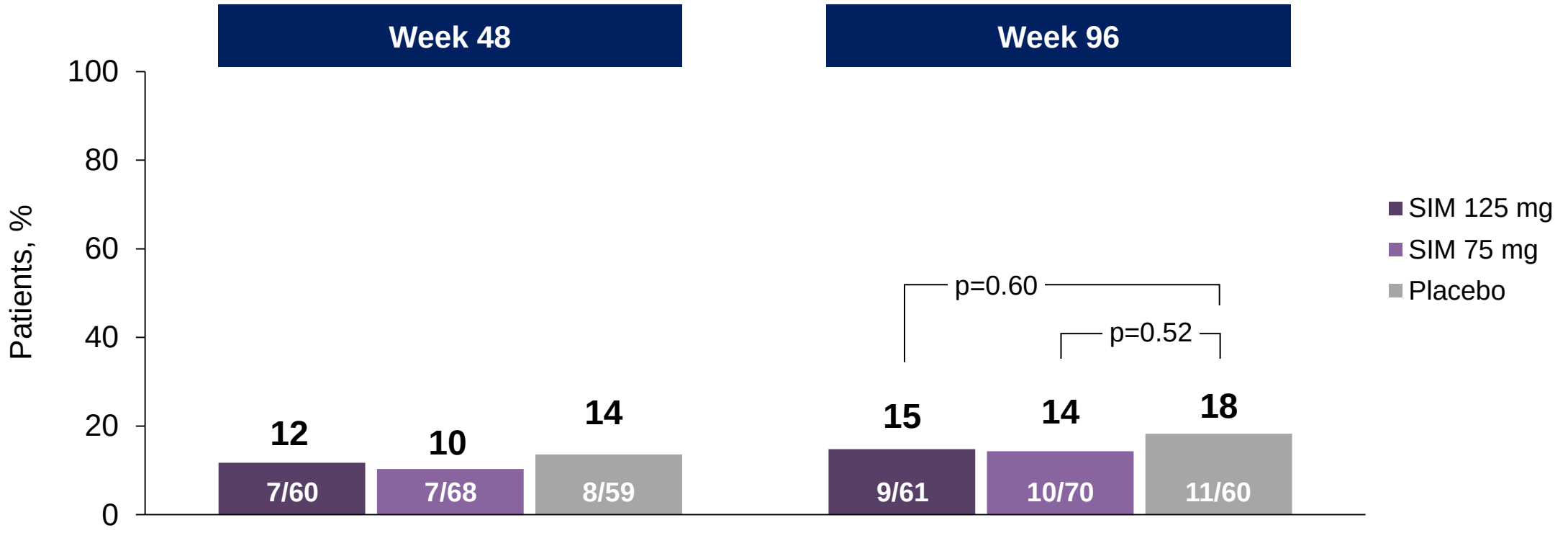
BL, baseline.

Results: No Effect of SIM on Ishak Fibrosis Stage at Week 96



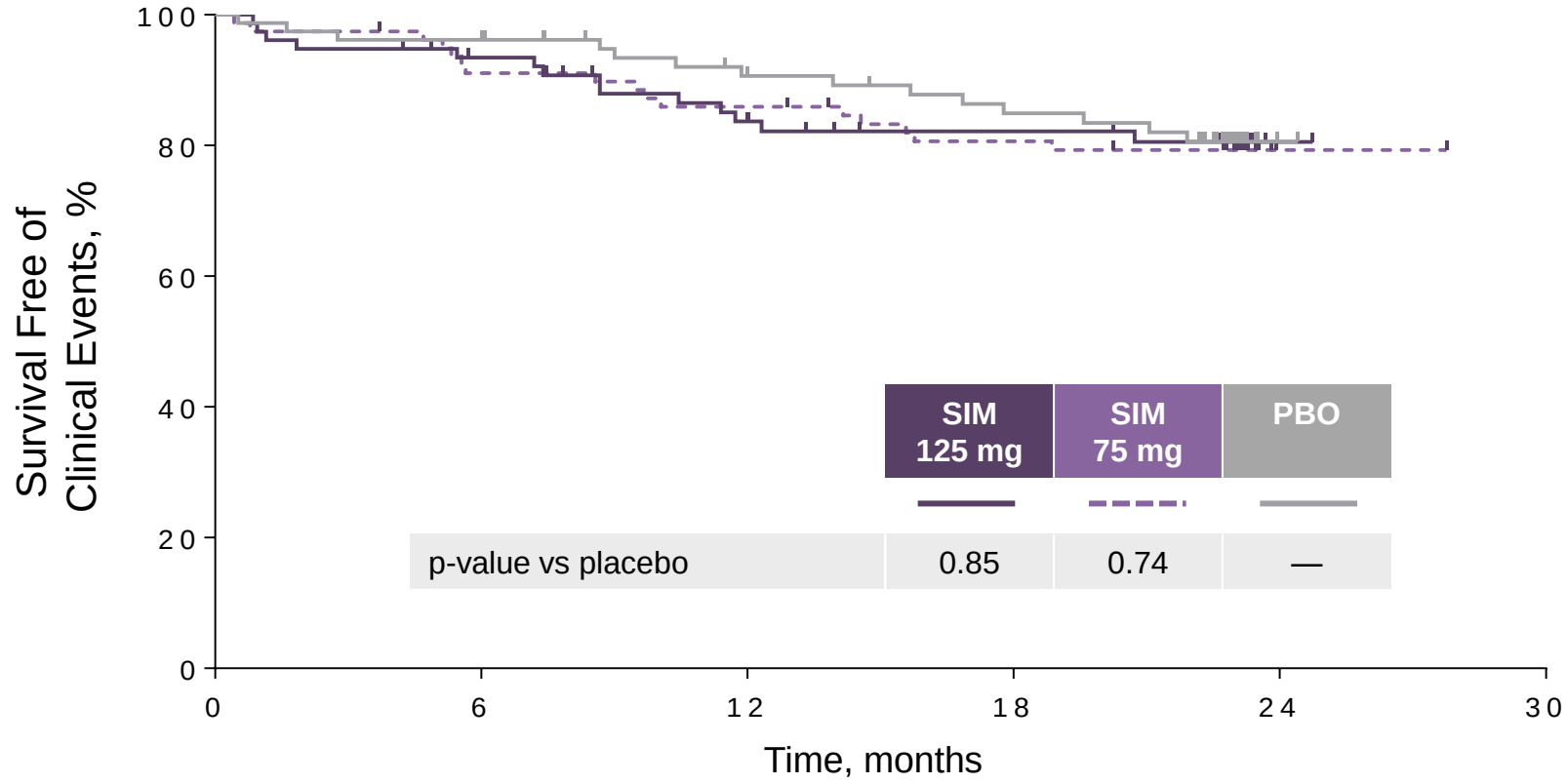
Data for patients with evaluable liver biopsies at baseline through Week 96 (last post-baseline value carried forward to Week 96 if biopsy missing).
p-values for comparison with placebo stratified for baseline sIgG4.
No effect of SIM on Enhanced Liver Fibrosis (ELF) score. Bowlus C, et al. EASL 2017 (#FRI-382).

Results: No Effect of SIM on Progression to Cirrhosis



Data for patients with F0–4 fibrosis at baseline and follow-up biopsies (last post-baseline value carried forward to Week 96 if biopsy missing).
p-values for comparison with placebo stratified for baseline sIgG4.

Results: No Effect of SIM on PSC-Related Clinical Events



Number at risk (n)

Placebo	78	75	64	59	1	0
SIM 125 mg	77	69	57	52	2	0
SIM 75 mg	79	71	67	61	1	0

p-value from stratified log-rank test.

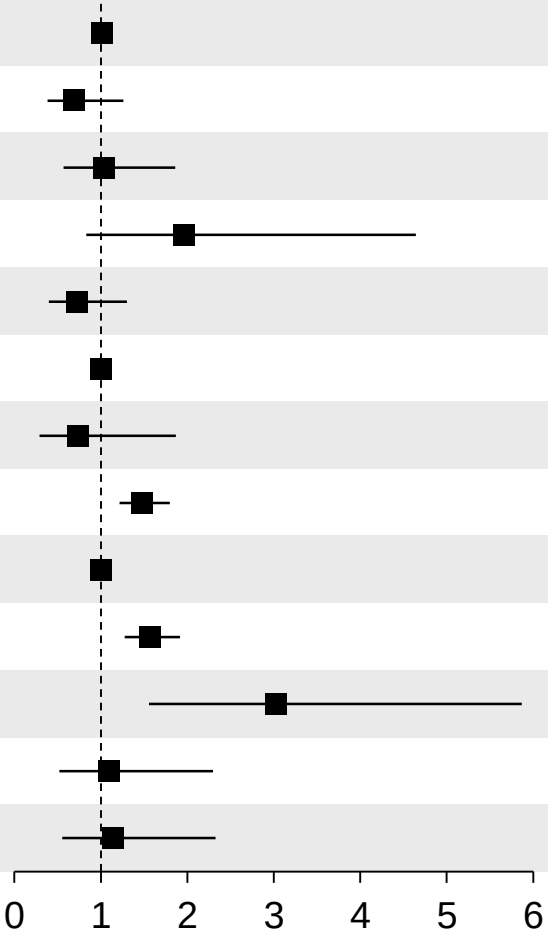
Results: No Effect of SIM on PSC-Related Clinical Events

Patients, n (%)	SIM 125 mg n=77	SIM 75 mg n=79	Placebo n=78
PSC Progression Events	14 (18)	16 (20)	14 (18)
Ascending cholangitis	8 (10)	11 (14)	7 (9)
Jaundice	3 (4)	3 (4)	3 (4)
Variceal hemorrhage	0	2 (3)	0
Ascites	1 (1)	1 (1)	0
Cholangiocarcinoma	1 (1)	0	2 (3)
Hepatic encephalopathy	1 (1)	0	1 (1)
Sepsis	0	0	2 (3)

Results: Baseline Predictors of PSC-Related Clinical Events

Univariate Analysis

	Hazard Ratio	95% CI	p-value
Age, *per year*	**1.01**	0.98, 1.04	0.54
Male	**0.69**	0.38, 1.26	0.23
Ulcerative colitis	**1.03**	0.57, 1.86	0.92
Intra- and extra-hepatic duct involvement on MRCP *	**1.96**	0.83, 4.64	0.12
UDCA treatment	**0.72**	0.38, 1.30	0.28
sLOXL2, *per pg/mL*	**1.00**	1.00, 1.00	**0.027**
IgG4 >140 mg/dL	**0.74**	0.29, 1.87	0.52
Bilirubin, *per mg/dL*	**1.48**	1.22, 1.80	**<0.001**
ALP, *per U/L*	**1.00**	1.00, 1.00	**<0.001**
ELF score	**1.56**	1.28, 1.92	**<0.001**
Ishak stage 3–6	**3.02**	1.56, 5.87	**0.001**
SIM 125 mg vs. placebo	**1.09**	0.52, 2.30	0.81
SIM 75 mg vs. placebo	**1.14**	0.55, 2.33	0.73



* Versus only intra-hepatic duct involvement.

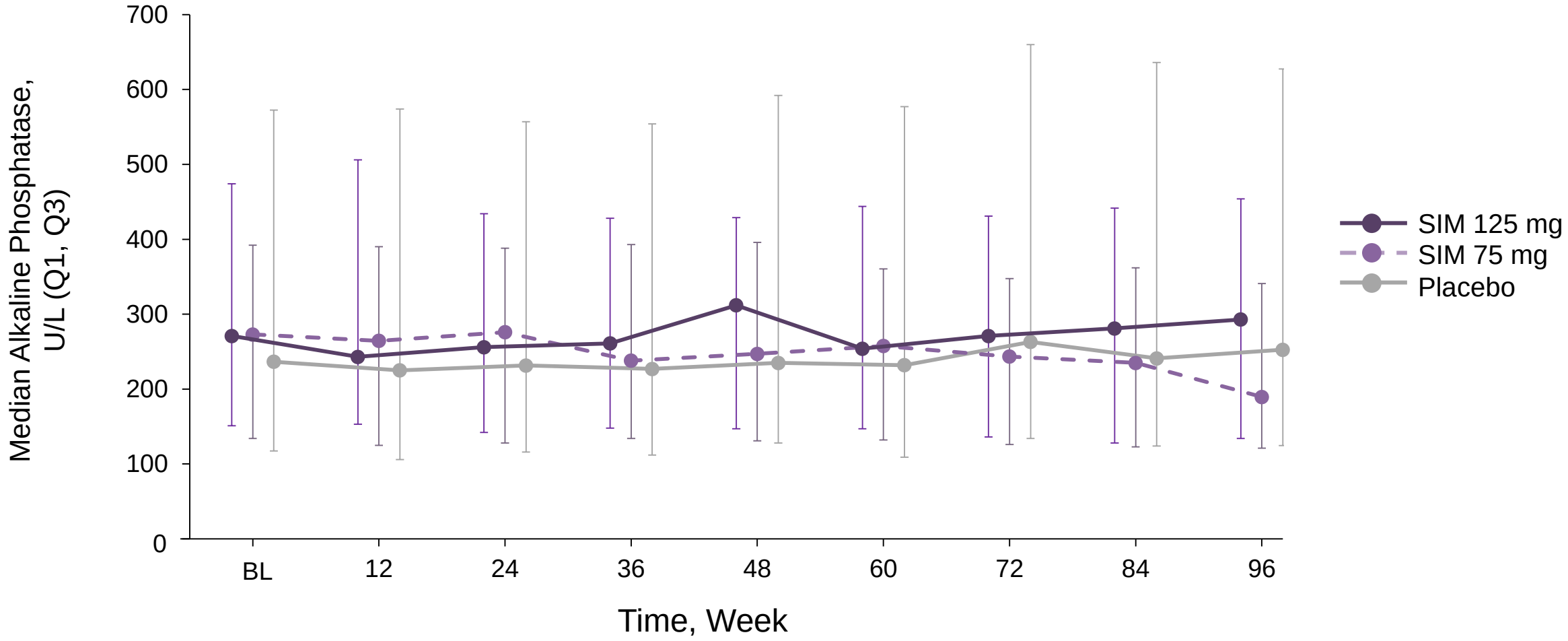
Results: Baseline Predictors of PSC-Related Clinical Events

Multivariate Analysis

	Hazard Ratio	95% CI	p-value
ALP, *per U/L*	**1.00**	1.00, 1.00	0.013
ELF score	**1.31**	1.00, 1.71	0.046
Ishak stage 3–6	**1.98**	1.96, 4.06	0.063
SIM 125 mg vs. placebo	**1.19**	0.56, 2.54	0.65
SIM 75 mg vs. placebo	**1.36**	0.65, 2.86	0.42

Stepwise Cox regression analysis with treatment assignment forced into the model.

Results: No Effect of SIM on Serum ALP



Levy C, et al. EASL 2017 (#FRI-386).

Results: Safety

Patients, n (%)	SIM 125 mg n=77	SIM 75 mg n=79	Placebo n=78
AE	74 (96)	75 (95)	78 (100)
Grade 3–4 AE	27 (35)	25 (32)	31 (40)
Serious AE	23 (30)	16 (20)	21 (27)
Treatment-related SAE	2 (3) *	2 (3) †	0
Treatment D/C due to AE	6 (8)	4 (5)	8 (10)
Death	0	0	0
Grade 3–4 lab abnormality	46 (60)	47 (60)	44 (56)

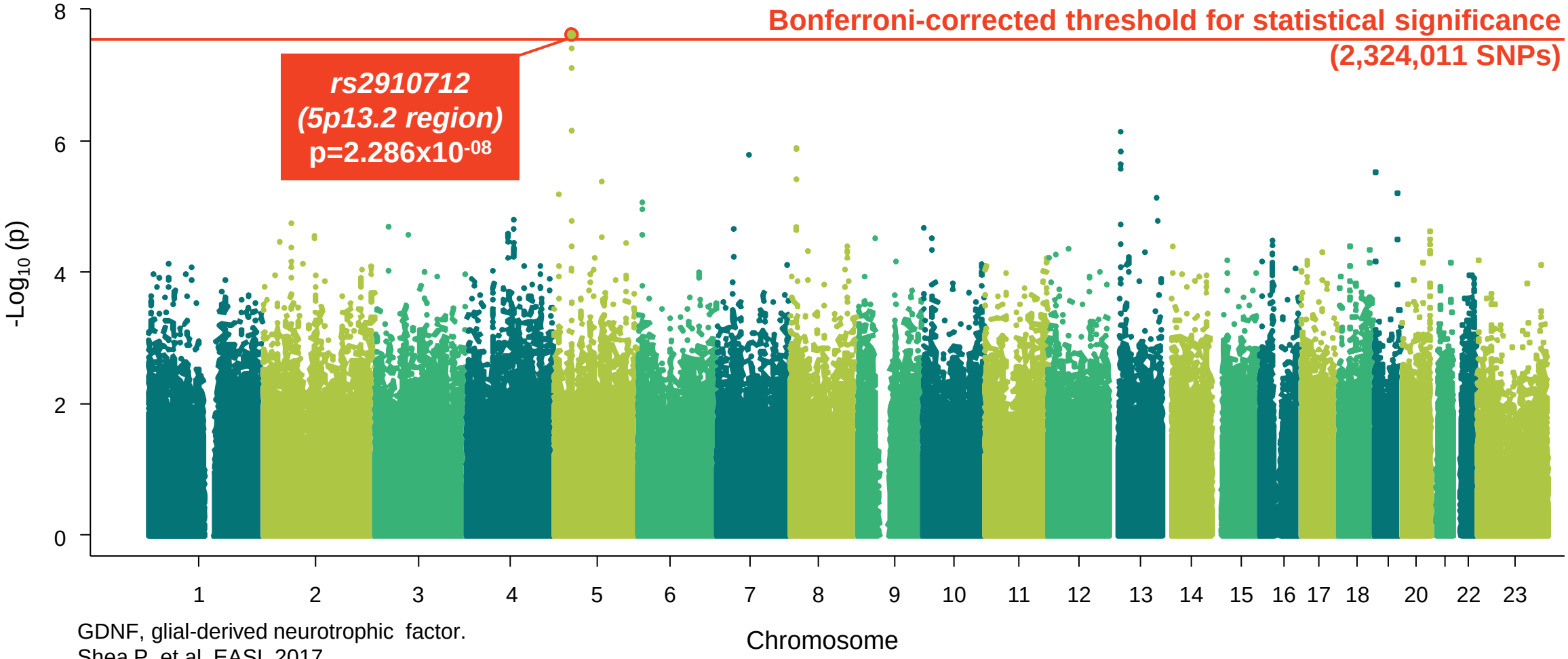
* Colitis, increased liver biochemistry (Grade 3 ALT/AST).
† Ventricular tachycardia, benign biliary neoplasm.

Additional Lessons Learned

1	GWAS
2	Prognostic impact of ALP
3	Histology
3	Transient elastography
5	Serum fibrosis markers
6	MRCP

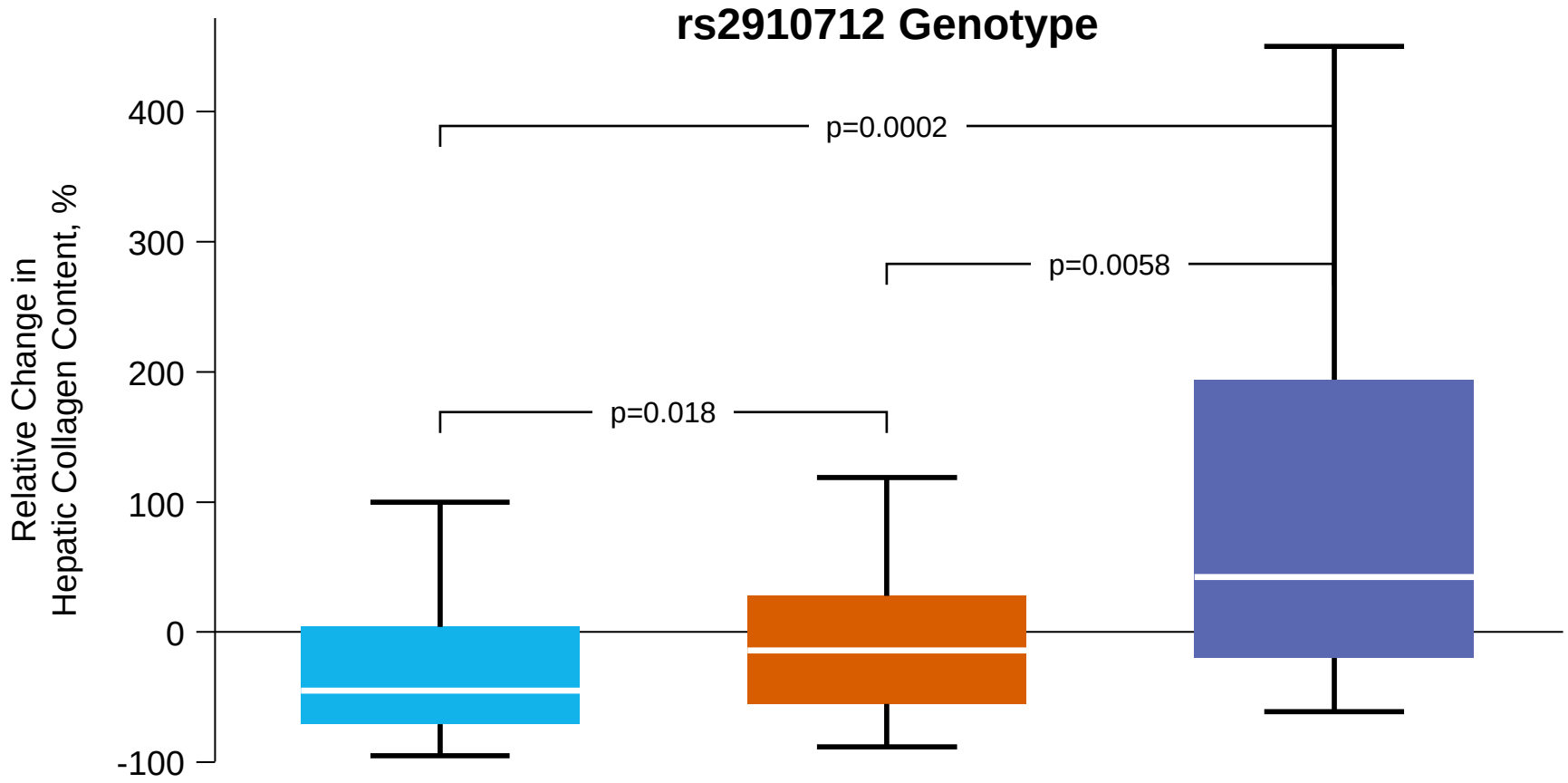
GWAS Identified One Unique Region Near *GDNF* Associated with Progressive Fibrosis

Manhattan Plot of Significance Scores from Linear Regression Analysis of *Relative Change in Hepatic Collagen Content* at Week 96 (Mixed Ethnicities)



GDNF, glial-derived neurotrophic factor.
Shea P, et al. EASL 2017.

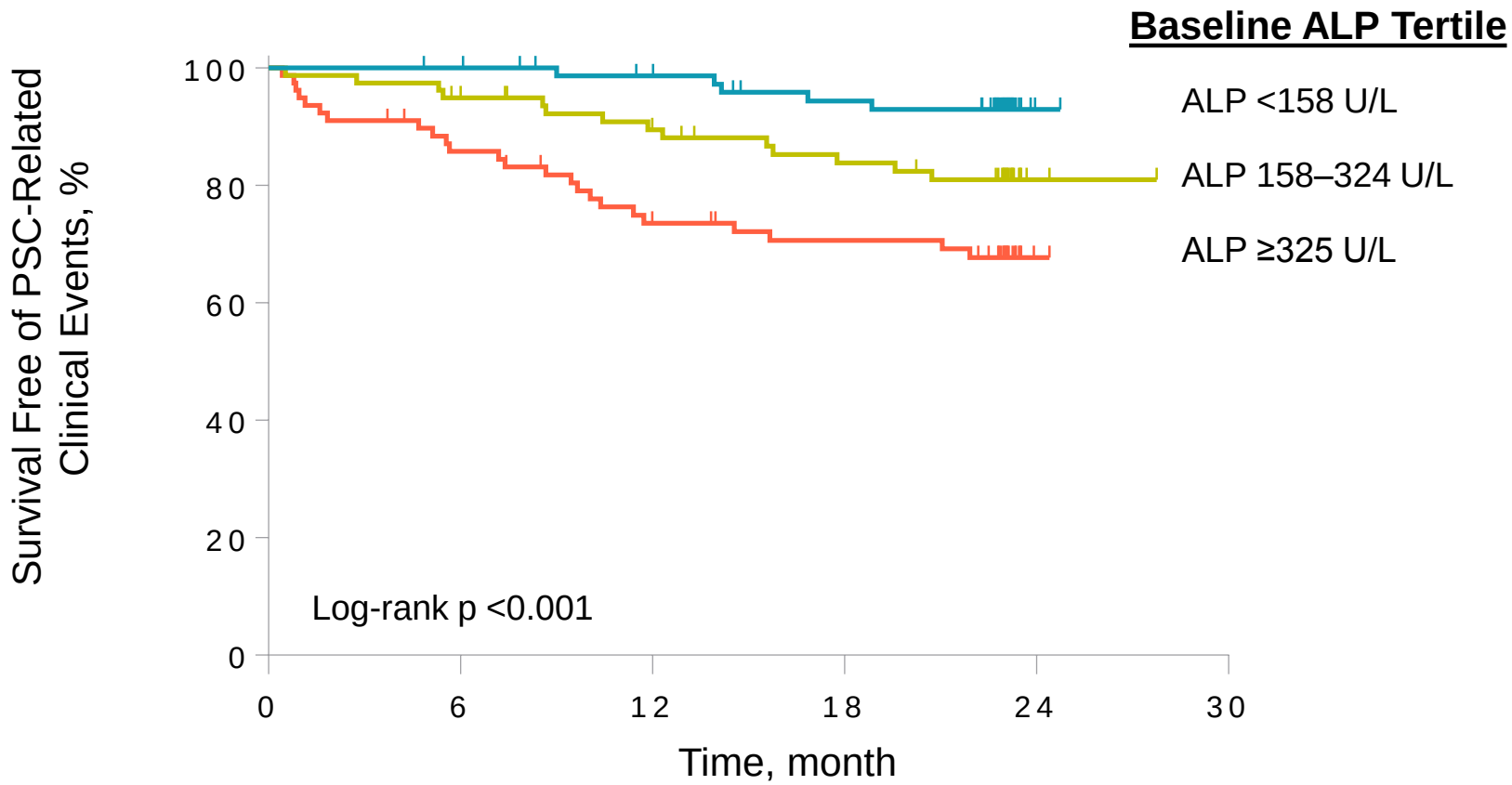
AA Minor Allele at rs2910712 is Associated with Increased Change in Hepatic Collagen at Week 96



	GG	AG	AA
	n=50	n=103	n=23
Median Change in Collagen (IQR), %	-45.0 (-70.7, 3.8)	-14.2 (-55.6, 27.7)	42.1 (-21, 200)

P-values determined by Mann-Whitney test.

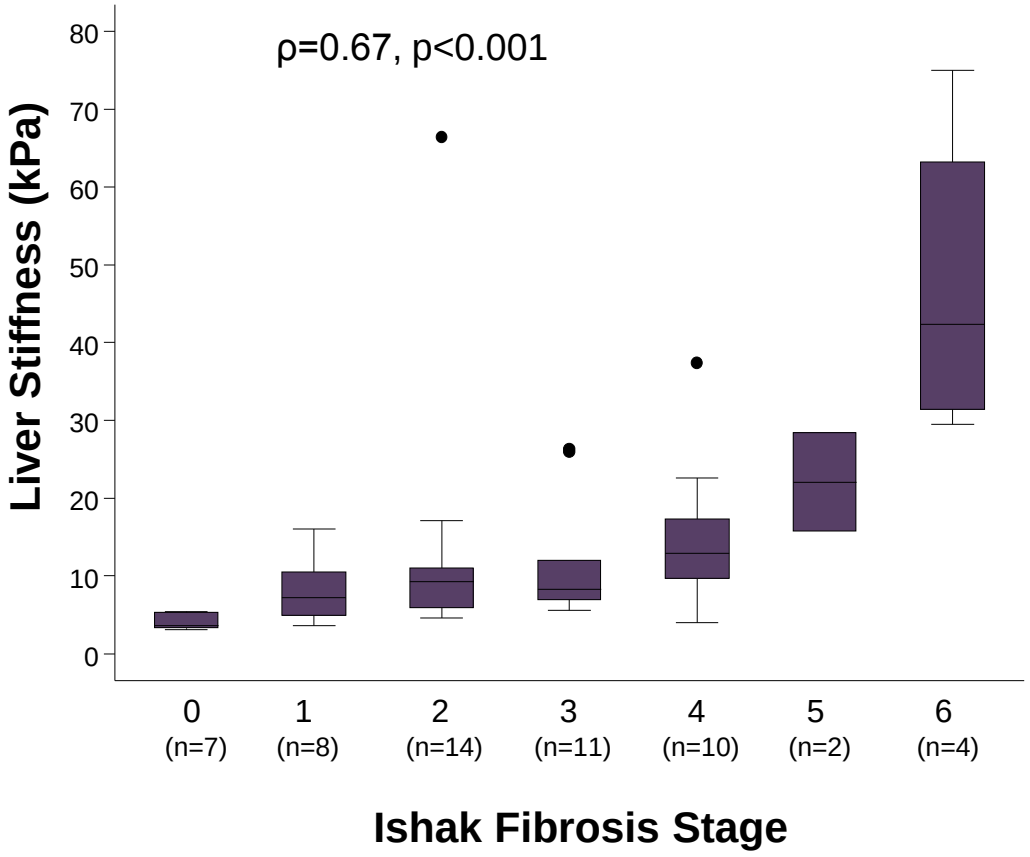
ALP at Baseline, Not its Change, Associated with PSC Disease Progression



- AUROC 0.70 for prediction of clinical events

AUROC, area under receiver operating characteristic curve.
Levy C, et al. EASL 2017 (Abstr #FRI-386).

Transient Elastography for Prediction of PSC-Related Fibrosis



	AUROC (95% CI)	Cutoff (kPa) *	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Bridging Fibrosis (F0-2 vs. F3-6)	0.79 (0.67-0.91)	≥9.6	67 (46-83)	72 (53–87)	69 (48-86)	70 (51-85)
Cirrhosis (F0-4 vs. F5-6)	0.95 (0.88–1.00)	≥14.4	100 (54–100)	82 (69-91)	40 (16–68)	100 (91–100)

Bowlus CL, et al. EASL 2016 (Abstr #FRI-375).

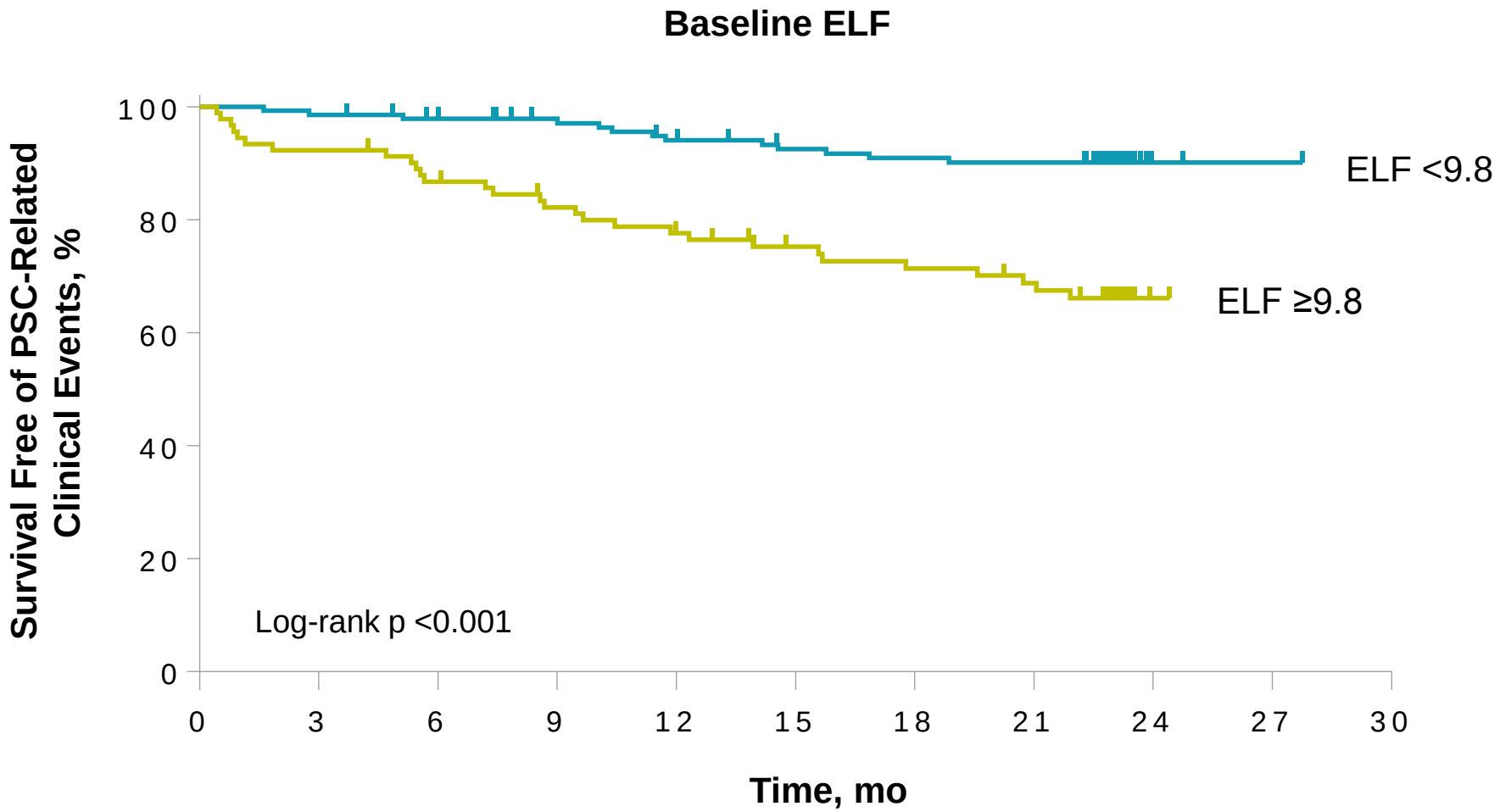
Serum Fibrosis Markers Effectively Exclude PSC-Related Cirrhosis

Test	AUROC	Cut-off *	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
sLOXL2	0.81 (0.71-0.90)	≥164	67 (45-84)	85 (80-90)	35 (21-50)	96 (92-98)
APRI	0.81 (0.71-0.91)	>2.0	38 (19-59)	97 (93-99)	56 (30-80)	93 (89-96)
FIB-4	0.81 (0.70-0.91)	>3.25	26 (15-39)	99 (96-100)	88 (64-98)	80 (74-85)
FibroTest	0.84 (0.76-0.92)	≥0.73	58 (37-78)	91 (86-95)	44 (26-62)	95 (91-98)
ELF	0.82 (0.73-0.91)	≥9.8	79 (58-93)	64 (57-71)	21 (13-30)	96 (92-99)

- AUROCs sub-optimal for prediction of bridging fibrosis (0.62-0.77)

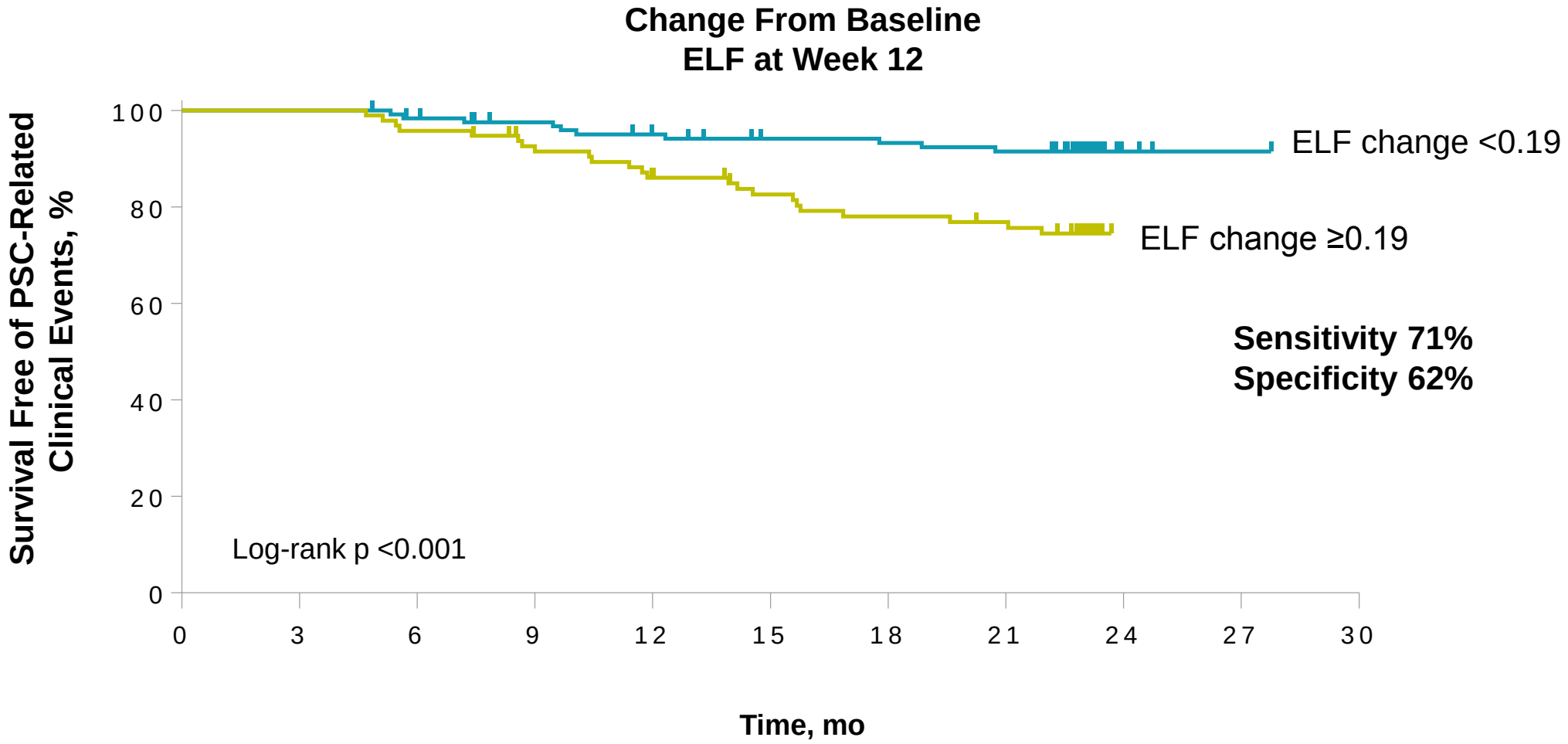
Bowlus CL, et al. EASL 2015 (Abstr #FRI-624).

Prognostic Significance of ELF



Bowlus CL, et al. EASL 2017 (Abstr #FRI-382).

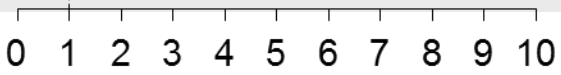
Prognostic Significance of ELF



Bowlus CL, et al. EASL 2017 (Abstr #FRI-382).

Prognostic Significance of MRCP

	HR (95% CI)	p-value	β Coefficient
Hepatic dysmorphy *	**3.11** (1.22, 7.92)	**0.018**	**1.13**
Portal hypertension	**2.31** (1.28, 4.17)	**0.005**	**0.84**
Peri-hepatic lymph nodes	**2.14** (1.20, 3.81)	**0.010**	**0.76**

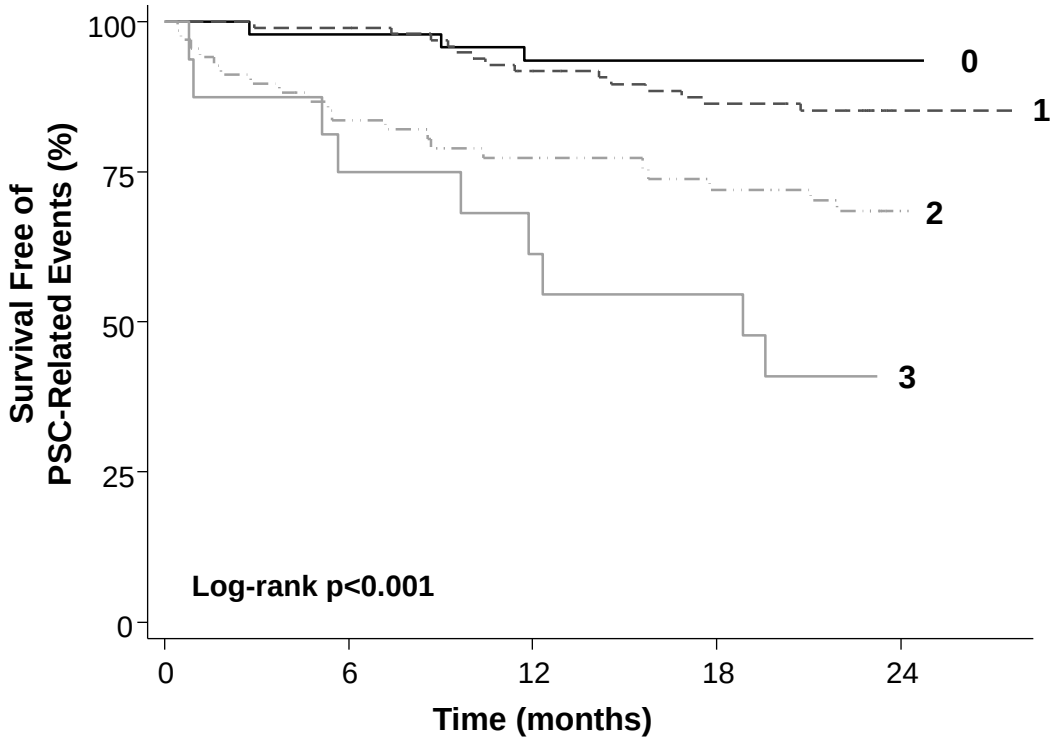


MRCP Risk Score (MRCP-RS)

= 1 x Hepatic dysmorphy + 1 x Portal HTN + 1 x Perihepatic nodes

Hepatic dysmorphy = liver atrophy, caudate lobe hypertrophy, and/or marked lobulation of the liver contour.
Multivariate Cox regression with backward selection ($p<0.05$ for variable retention).
Muir AJ, et al. AASLD 2017 (Presidential Plenary Presentation #140).

Prognostic Significance of MRCP



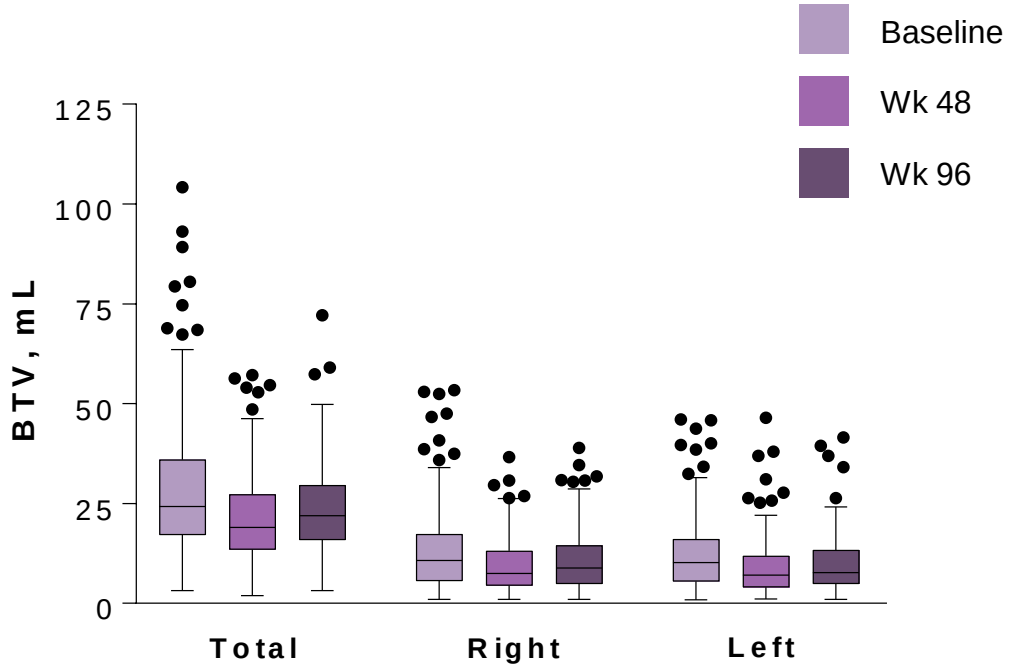
MRCP-RS	PSC-Related Events	Hazard Ratio (95% CI)
0	6% (3/48)	Ref
1	14% (14/101)	2.28 (0.65, 7.92)
2	30% (21/69)	6.05 (1.80, 20.30)
3	56% (9/16)	12.46 (3.37, 46.10)

- c-statistic of MRCP-RS for PSC-related clinical events, 0.71 (95% CI 0.63, 0.79)
- MRCP-RS associated with clinical events (HR 2.09; 95% CI 1.44, 3.04) after adjustment for baseline serum ALP and ELF

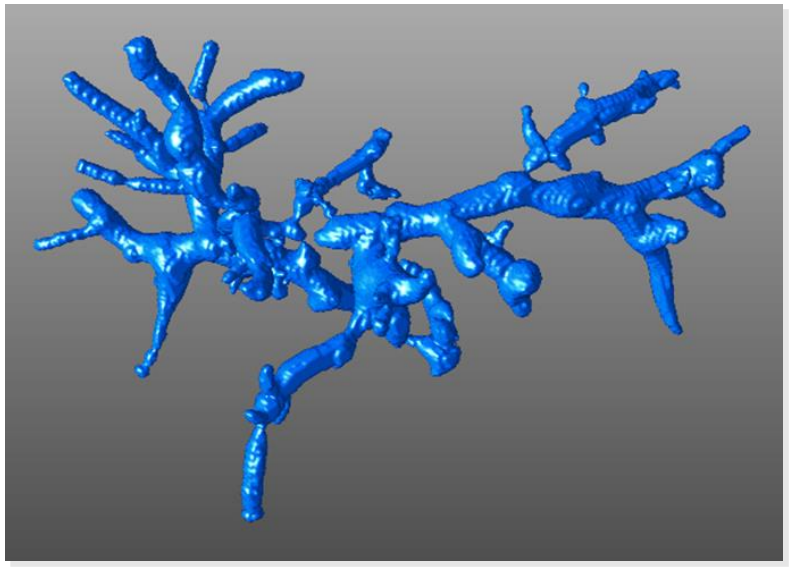
Muir AJ, et al. AASLD 2017 (Presidential Plenary Presentation #140).

Quantification of Biliary Tree Volume in PSC:

3D Reconstruction of 2D MRCP



Bile duct volume, 29.4 mL



- Baseline BTV associated with MRCP parameters (not prognosis) and decreased over time
  - Extensive biliary stricturing, intraductal stones, signs suspicious for cholangiocarcinoma, caudate lobe hypertrophy, and heterogeneity on T2W sequences

BL, baseline; BTV, biliary tree volume.
Tempany-Afdhal C, et al. AASLD 2017 (Abstr #292).

Conclusions

- SIM was safe and well-tolerated in patients with PSC
- After 96 weeks of treatment, SIM does not improve fibrosis or reduce PSC-related clinical events
- Data from this clinical trial provide important information regarding the natural history and management of PSC

Acknowledgments

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