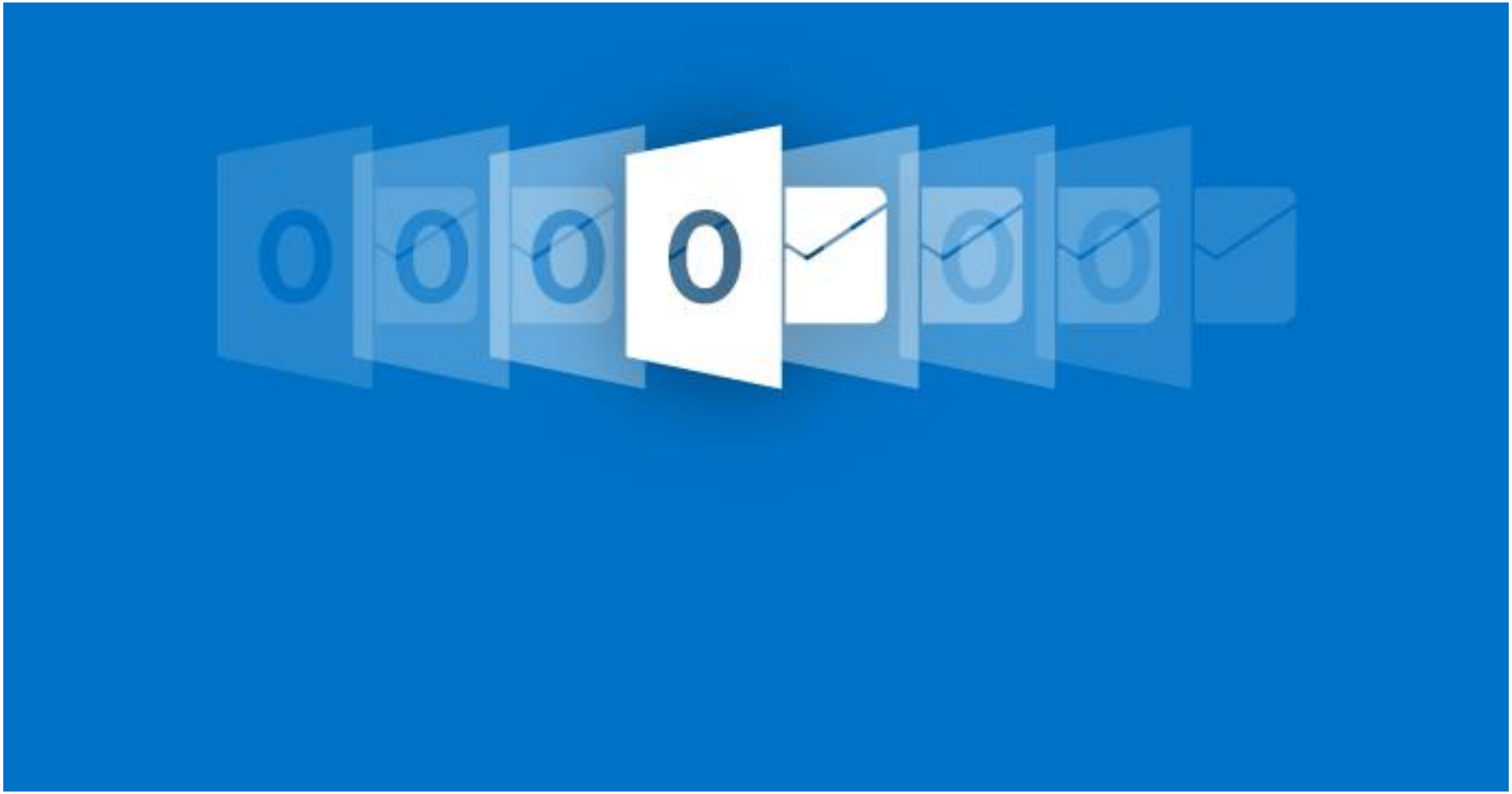
Clinical trial outlook



Primary sclerosing cholangitis industry drug development pipeline

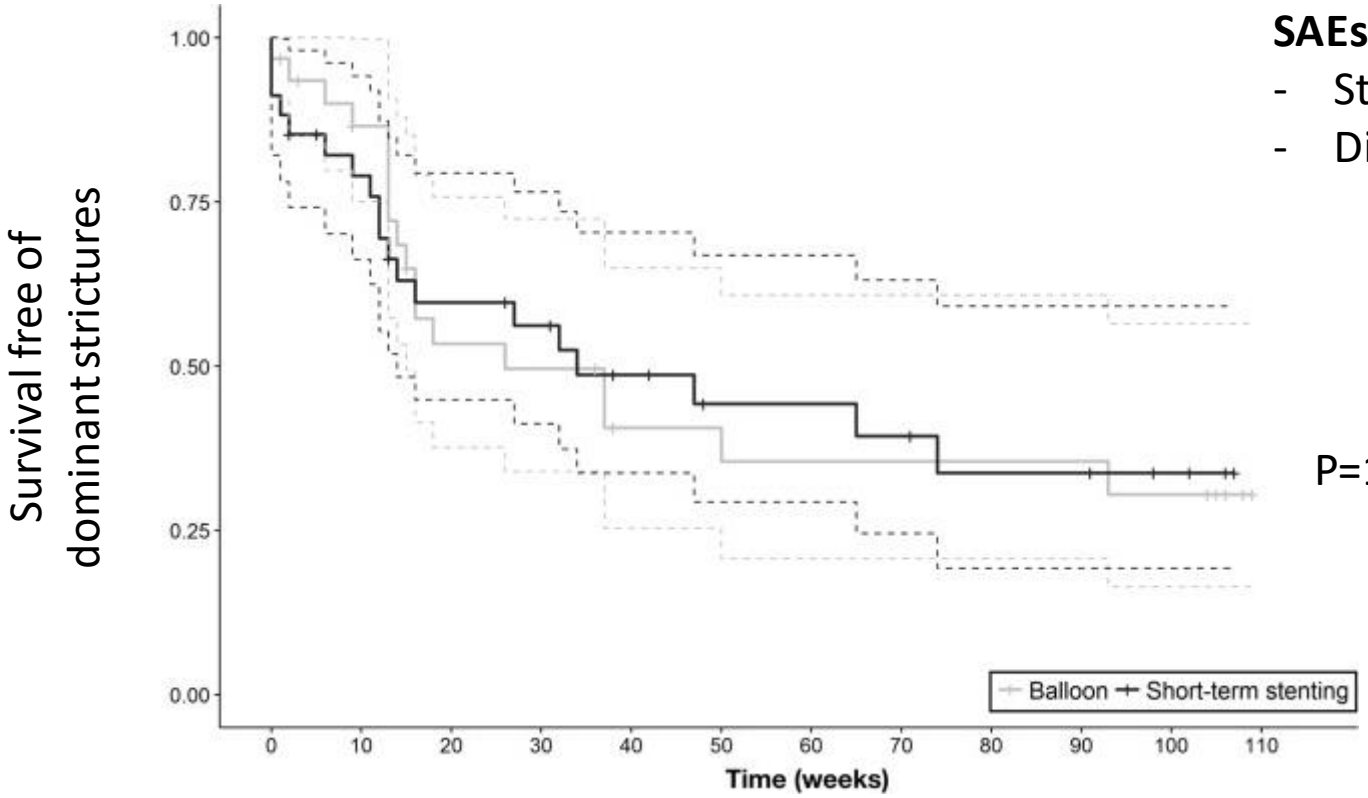
Preclinical		Phase I	Phase II	Phase III
			Volixibat potassium **Mirum Pharmaceuticals** *IBAT inhibitor*	
Vedolizumab **Takeda Evotec** *a4b7 integrin agonist*			Berberine ursodeoxycholate **HighTide Therapeutics** *Unspecified*	
GRI-0124 **GRI Bio** *NKT cell stimulant*	HM-15211 **Hanmi Pharmaceutical** *GLP-1/GIP/GCG agonist*	SCO-240 **Scohia Pharma** *SSTR5 antagonist*	CM-101 **Chemomab/Abzena** *CCL24 antagonist*	
H-01 **Halo Biosciences** *Hyaluronan synthase inhibitor*	Metabolic and infectious disease therapy **CD3 Centre for Drug Design** *IBAT inhibitor*	A-3907 **Albireo Pharma** *IBAT inhibitor*	HK-660S **Curome Biosciences** *NAD+ modulator*	
Rock2 Inhibitor **Angion Biomedica** *ROCK2 inhibitor*	odevixibat **Albireo Pharma/Jadeite Medicines** *IBAT inhibitor*	CS-0159 **Cascade Pharmaceuticals** *FXR agonist*	Orbcell-C **Orbsen Therapeutics** *IV MSC therapy*	
ST-003 **SteroTherapeutics** *GAL antagonist*	PSC therapy **Engitix Therapeutics** *Unspecified*	HPG-1860 **Hepagene Therapeutics** *FXR agonist*	PLN-74809 **Pilant Therapeutics** *a1b6 integrin antagonist*	
BX-002 **BiomX** *Microbiome modulator*	PV-201 **Parvus Therapeutics** *Unspecified*	INVA-8001 **Invea Therapeutics** *Immunosuppressant*	Seladelpar **CymaBay Therapeutics** *PPAR-d agonists*	Norursodeoxycholic acid **Dr. Falk Pharma/Eisai** *Cholesterol inhibitor*
Elafibranor **Genfit Ipsen** *PPAR-a/PPAR-d agonist*	setanaxib **Calliditas Therapeutics** *NADPH oxidase 1/4 inhibitor*	STP-707 **Sirnaomics** *TGF-β1/Cox-2 gene inhibition*	Vidofludimus calcium **Immunic 4SC** *DHODH inhibitor*	Cilofexor **Gilead/Phenex** *FXR agonist*

Trivedi (unpublished)

A note about clinical trials in PSC

- Heterogeneous intent-to-treat population
- Lack of validated surrogates of disease progression
- Most use serum ALP as primary endpoint
- Must learn from the negatives!

Stent or not to stent, that is the question…



SAEs:

- Stent: 45%
- Dilation alone: 6%

P=1.0

Ponsioen et al. Gastroenterology 2018

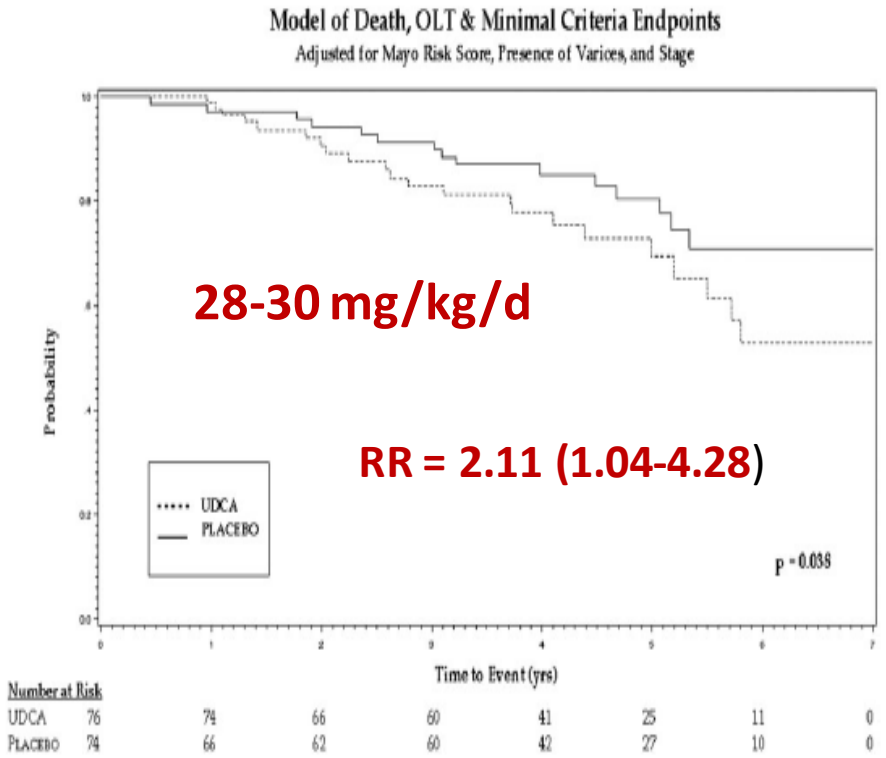
UDCA in PSC

Pilot study: 30 patients,
UDCA 25-30 mg/kg/d, 1 year

RESULTS: A marked improvement in serum alkaline phosphatase activity (1265 ± 172 *vs* 693 ± 110 U/L, $p < 0.001$), AST (161 ± 037 *vs* 77 ± 13 U/L, $p = 0.001$), albumin (4.0 ± 0.1 *vs* 4.2 ± 0.1 g/dl, $p = 0.03$), and total bilirubin (1.6 ± 0.3 *vs* 1.3 ± 0.2 mg/dl, $p = 0.1$) occurred at 1 yr of therapy with high-dose UDCA. Changes in the Mayo risk score after 1 yr of treatment were significantly different among the three groups ($p < 0.001$), and these changes would be translated into a significantly different expected survival at 4 yr ($p = 0.05$). This expected survival at 4 yr was significantly different between placebo and the dose of 25–30 mg/kg per day ($p = 0.04$).

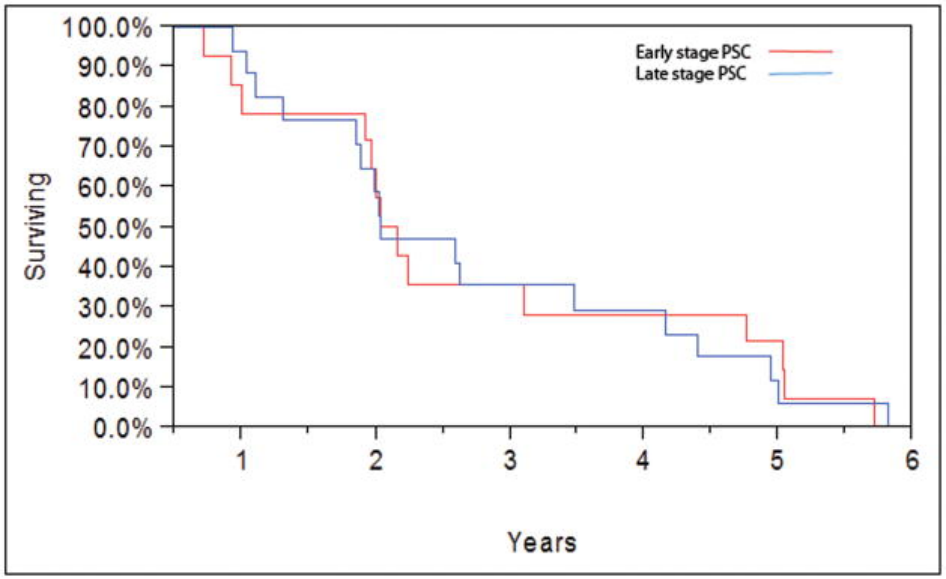
Harnois *et al.* Am J Gastroenterol 2001

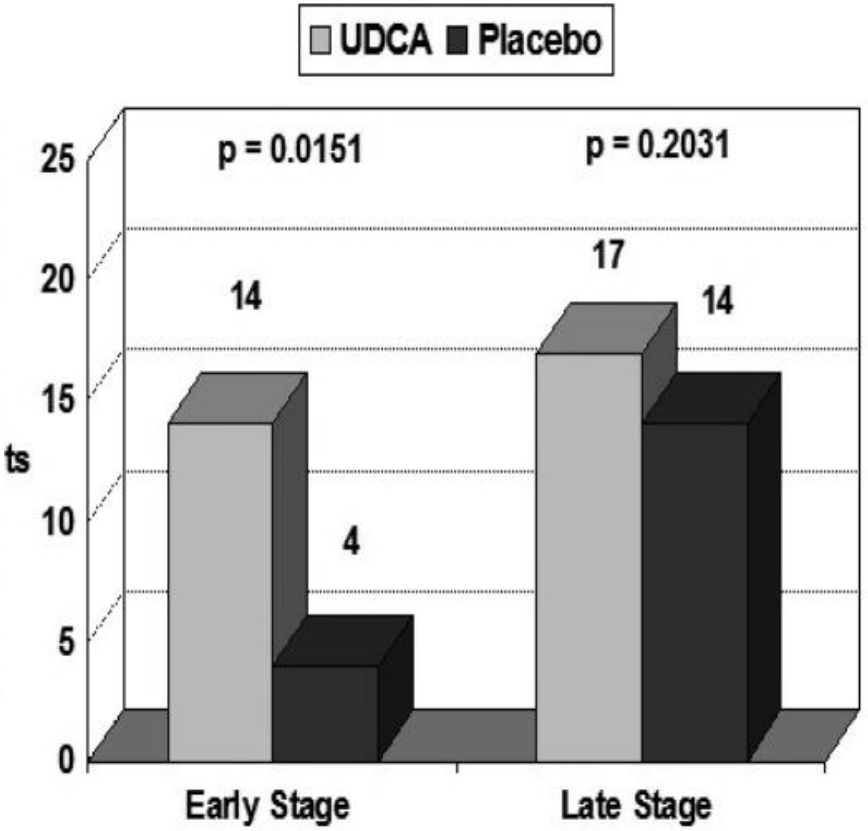
Randomised control trial



Lindor *et al*. Hepatology 2009

UDCA in PSC

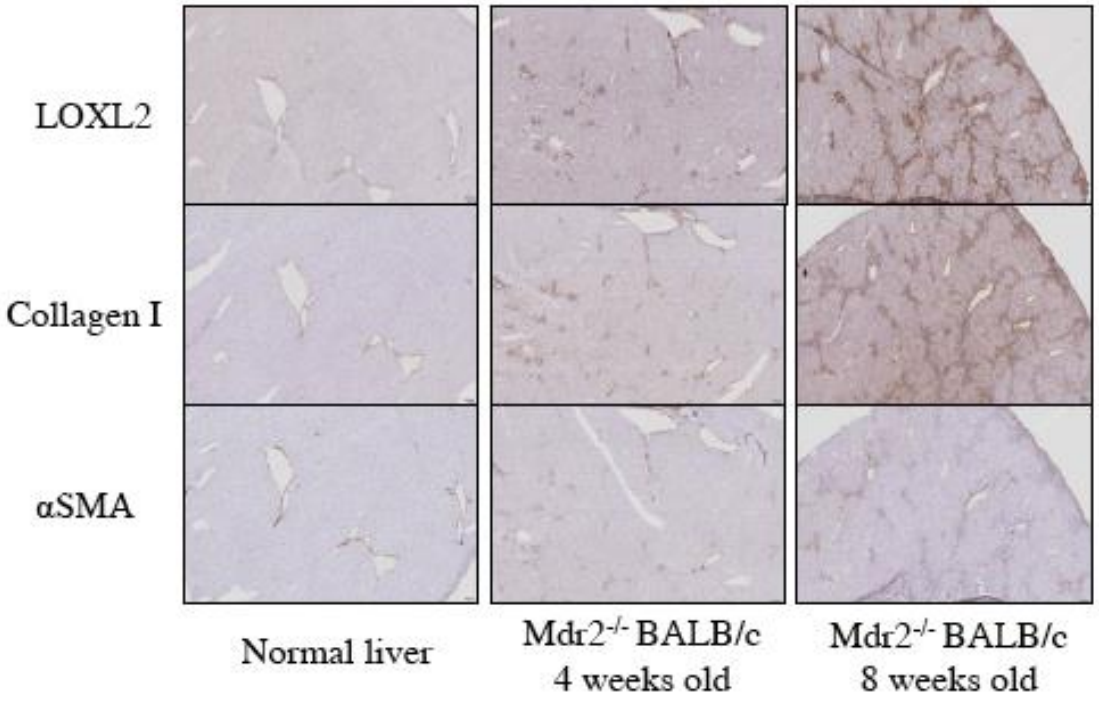




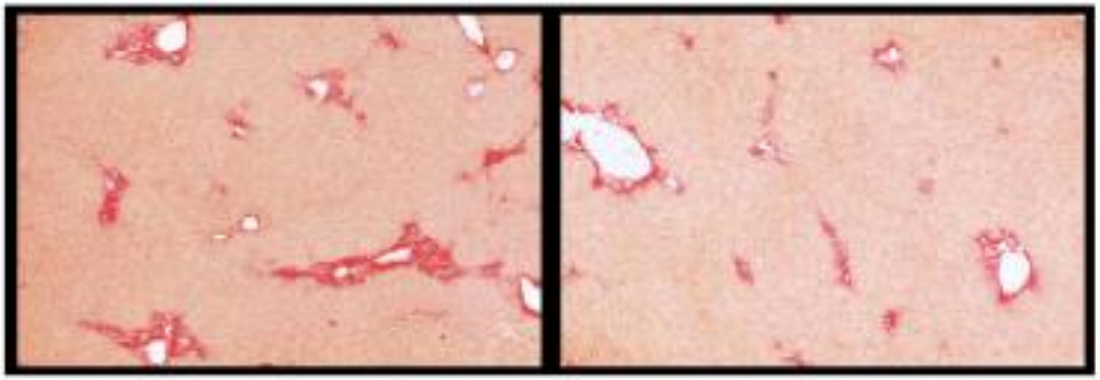
Imam *et al*. AP&T 2011

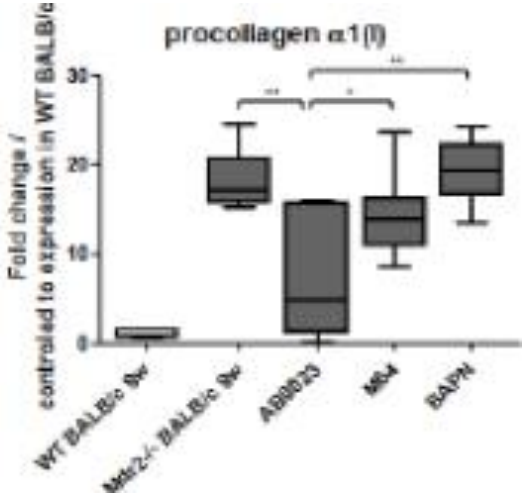
Targeting biliary fibrosis with anti- LOXL2 (simtuzumab):

Rationale:

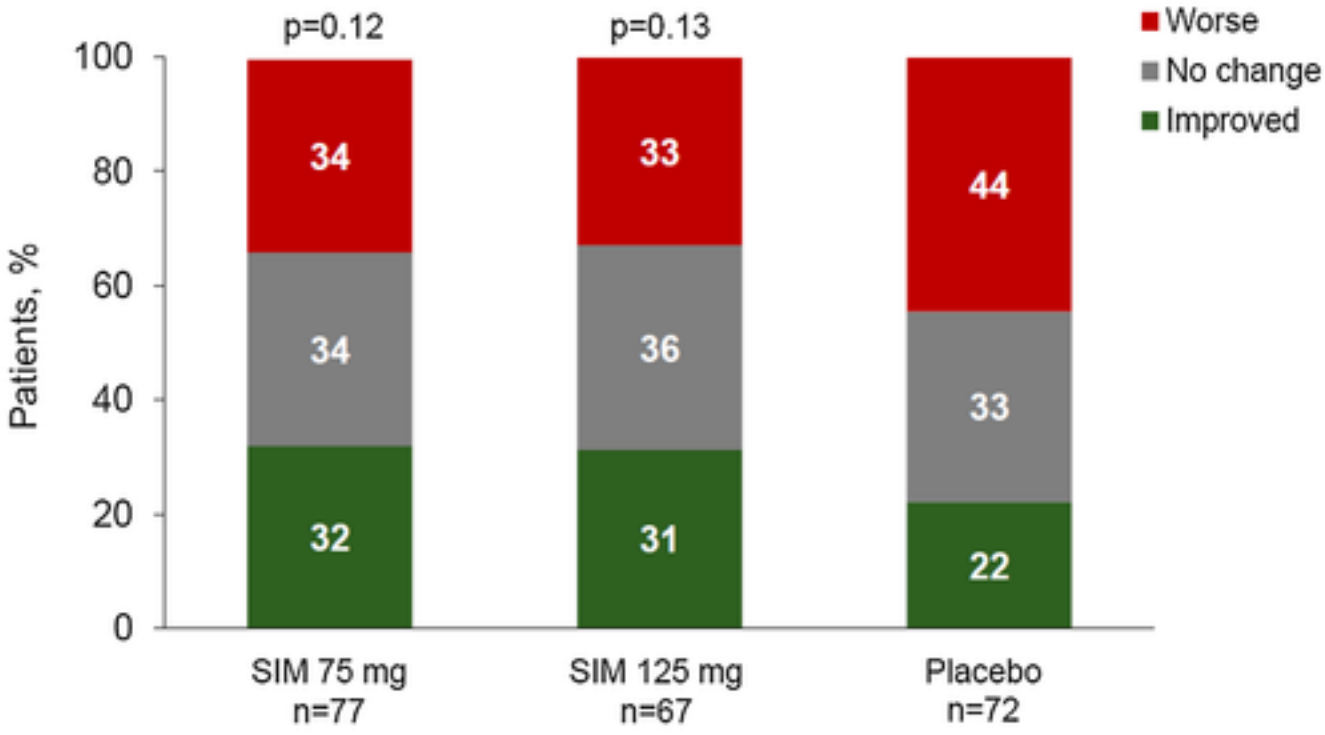


LOXL2 inhibition attenuates biliary fibrosis in the *Mdr2* $^{-/-}$ model of PSC

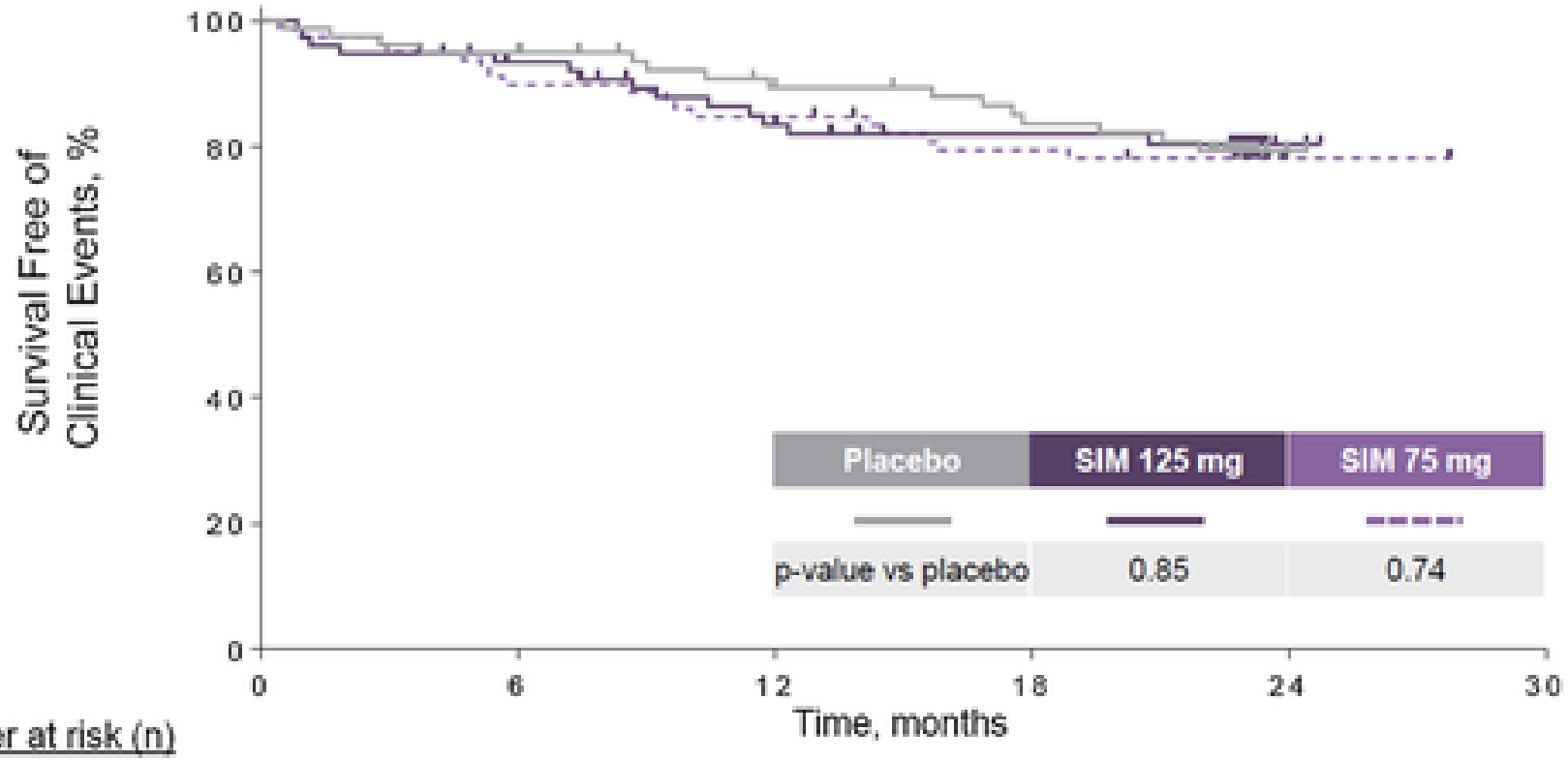




Anti-LOXL2 does not slow disease progression



Anti-LOXL2 does not slow disease progression

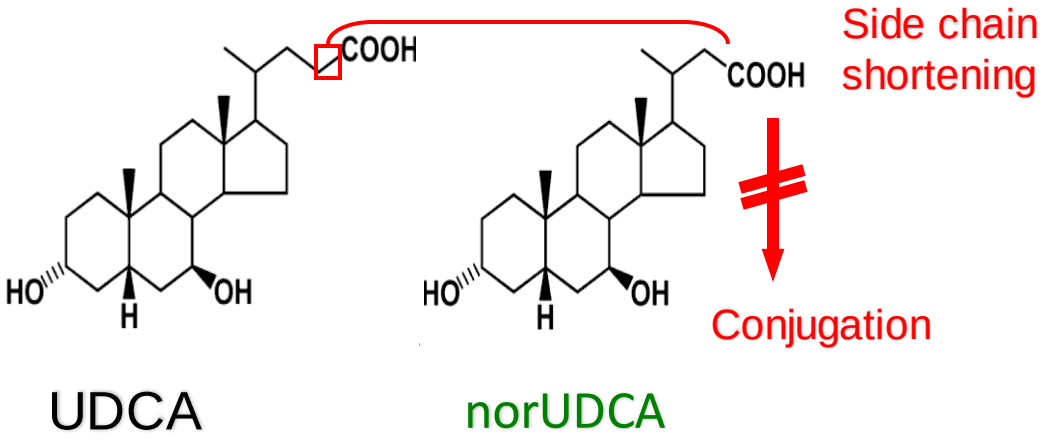


Number at risk (n)						
Placebo	78 (0)	74 (4)	63 (8)	58 (12)	1 (15)	0 (15)
SIM 125 mg	**77 (0)**	**69 (5)**	**56 (13)**	**51 (14)**	**2 (15)**	**0 (15)**
SIM 75 mg	79 (0)	70 (8)	66 (12)	60 (16)	1 (17)	0 (17)

Muir et al. Hepatology 2018

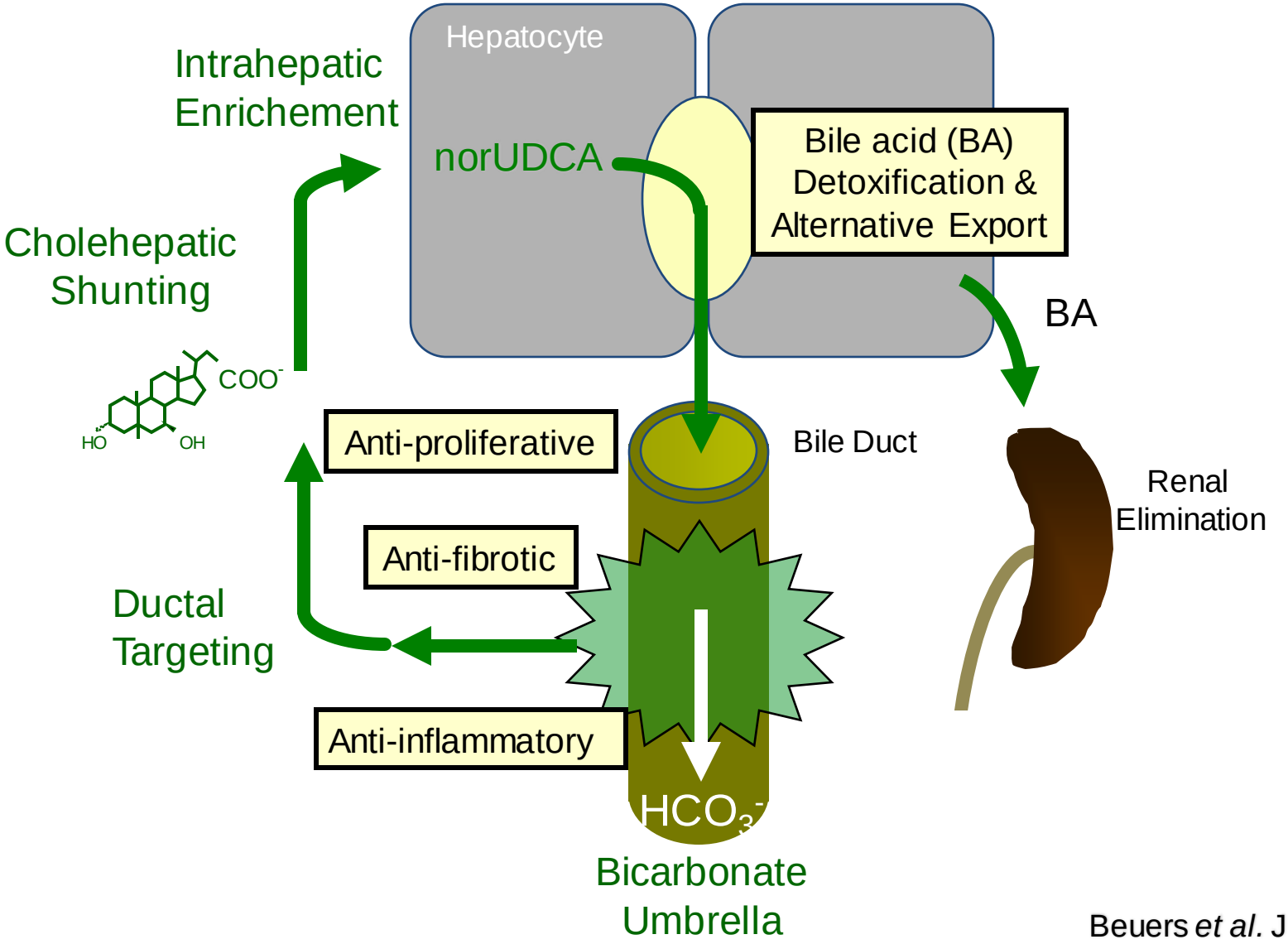
NorUDCA

- 24-*nor*-ursodeoxycholic acid (*nor*UDCA): side chain-shortened C_{23} homologue of UDCA



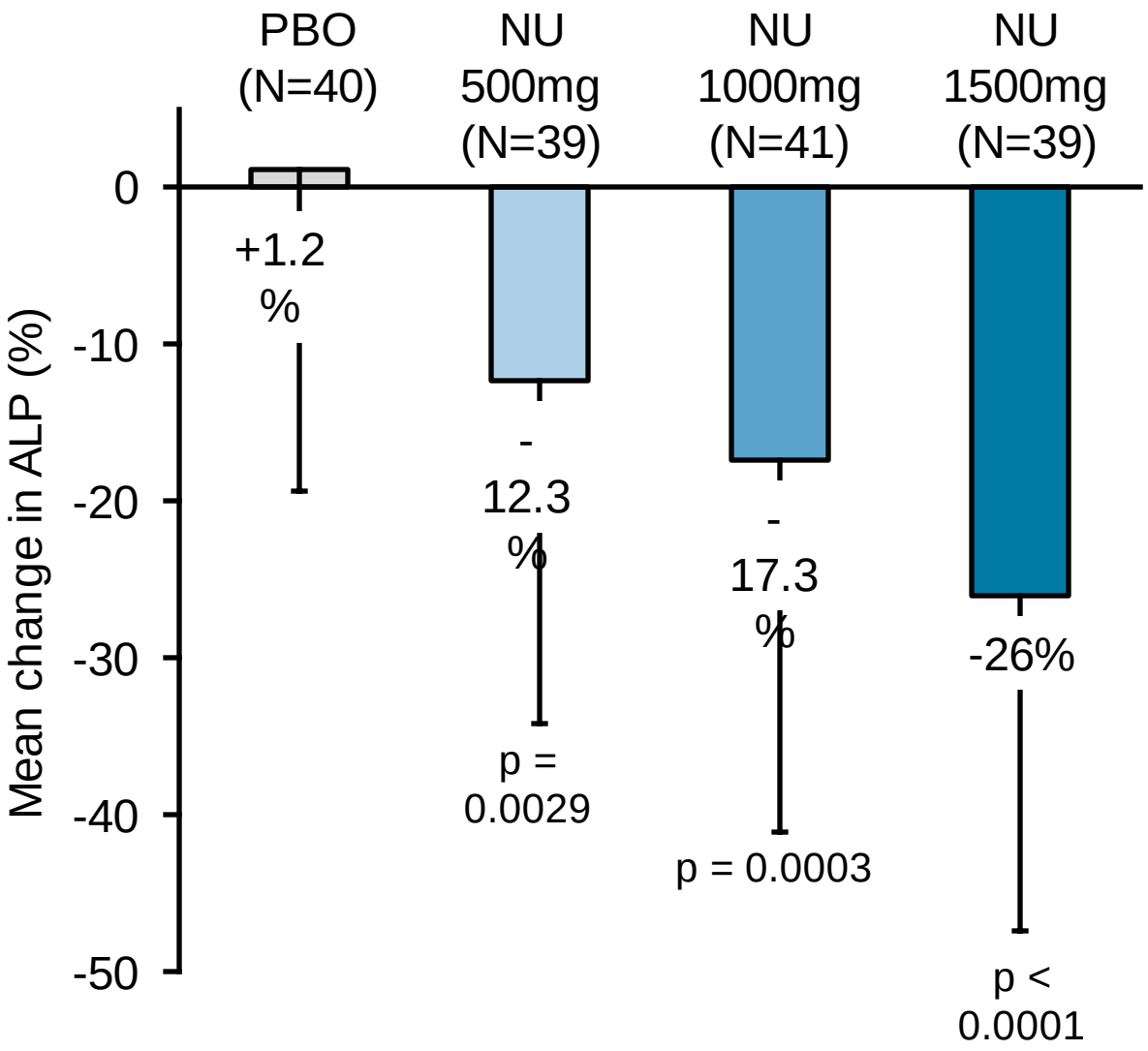
Yoon et al., *Gastroenterology* 1986
Hofmann et al., *Hepatology* 2005

NorUDCA: Mechanism of action



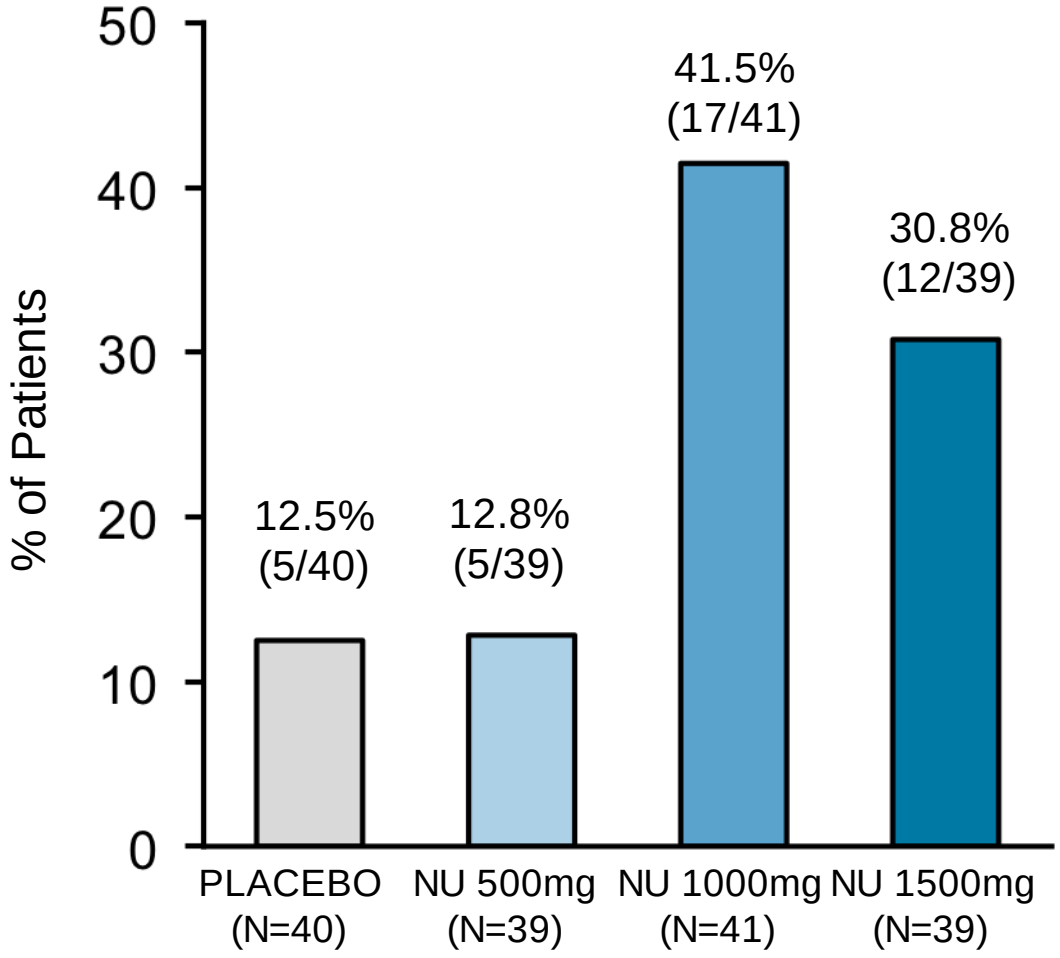
Beuers *et al.* J Hepatol 2015

Phase II clinical trial: results (I)



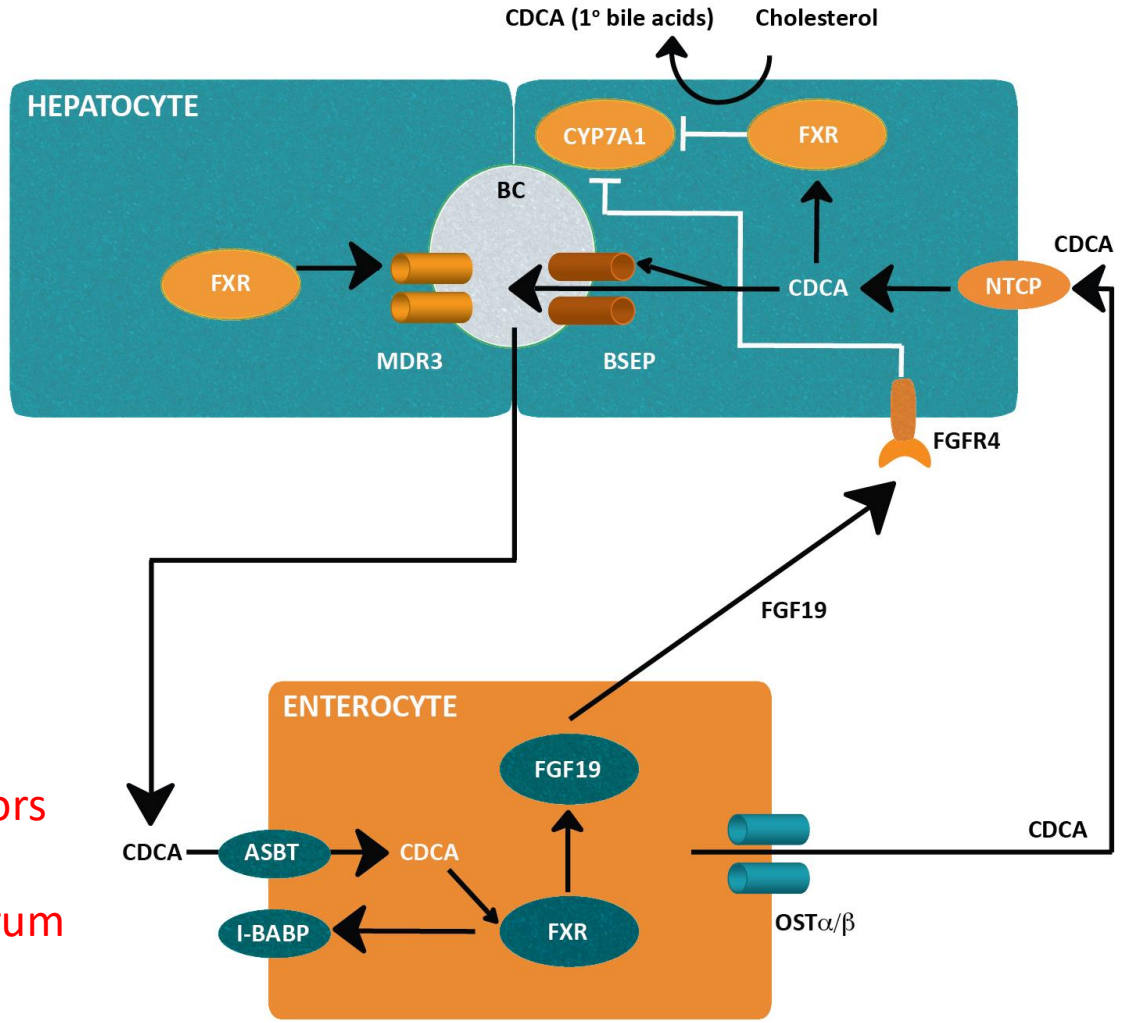
Fickert et al. J. Hepatol. 2017

Results (3): Patients (%) Reaching ALP ≤ 1.5 ULN (ITT)



Fickert et al. J. Hepatol. 2017

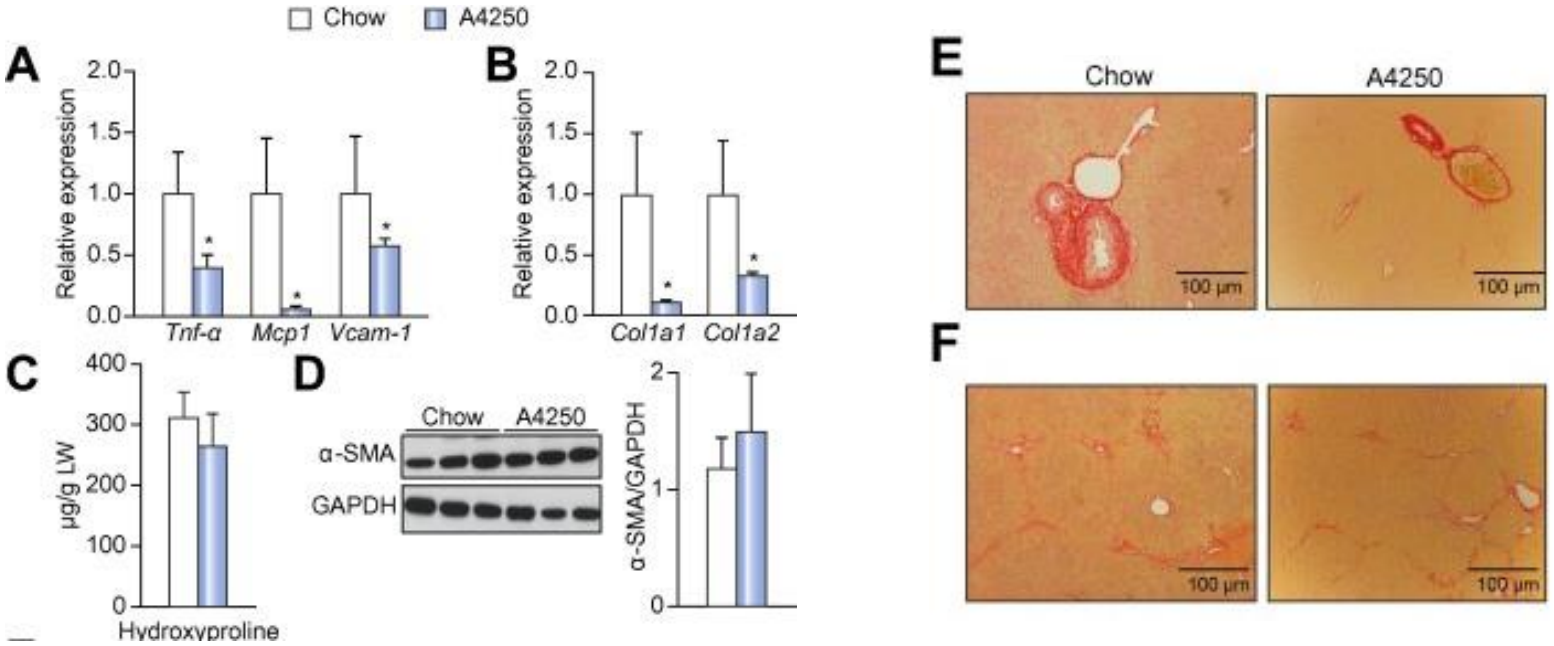
Bile acid pathway transporters…simplified



ASBT inhibitors for pruritus?
- P2 RCT; Mirum

Trivedi, *et al. Exp. Rev. Clin. Pharm.* 2016

ASBT inhibitors attenuate biliary fibrosis *in vivo*

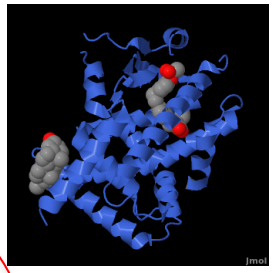


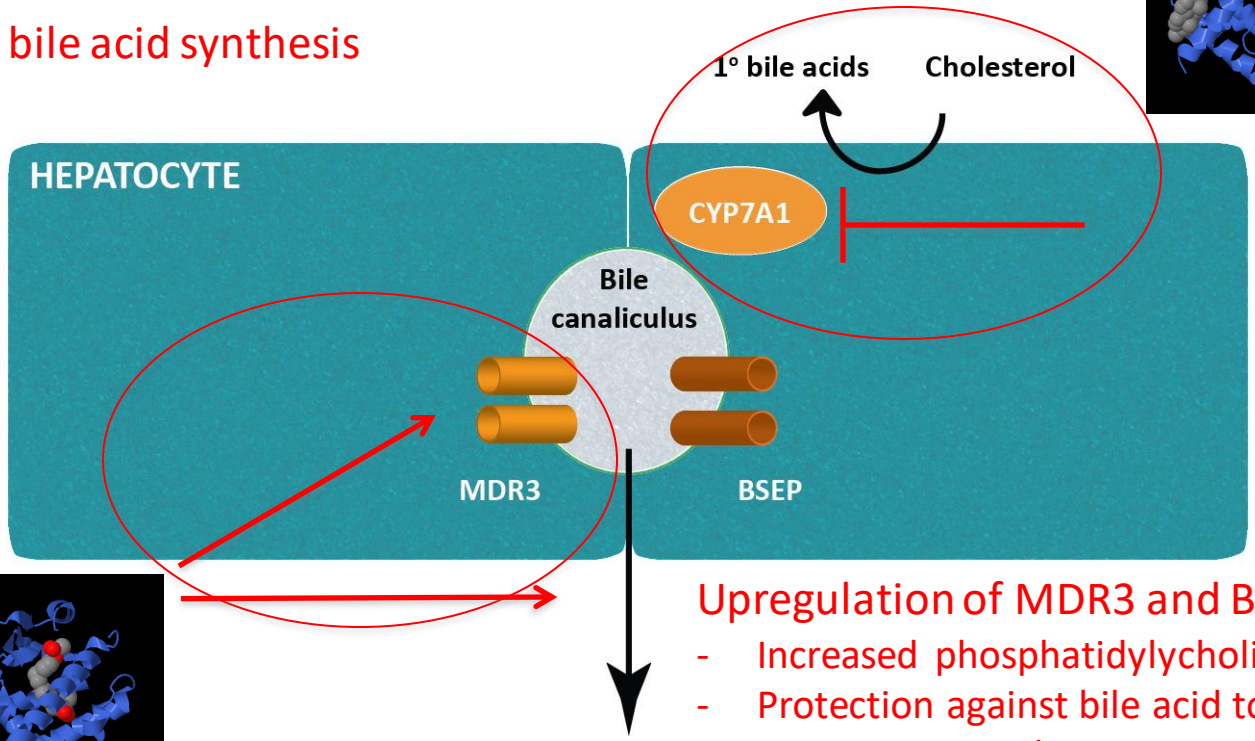
Mdr2 $^{-/-}$ **mice**

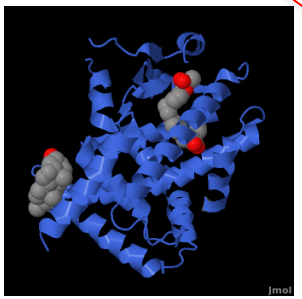
Baghdasaryan *et al*. J. Hepatol. 2015

Next generation PPAR agonists; IPSEN Elmwood Study

Inhibition of bile acid synthesis







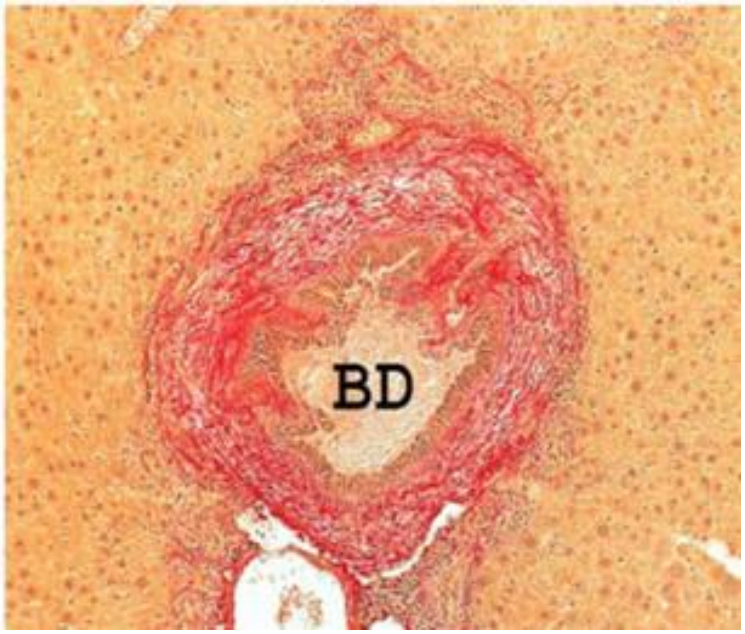
Upregulation of MDR3 and BSEP

- Increased phosphatidylycholine in bile
- Protection against bile acid toxicity

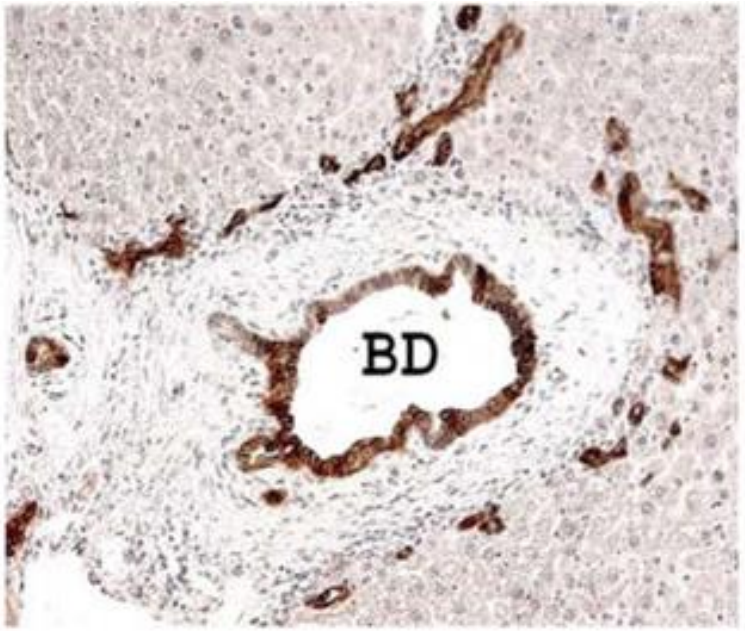
Anti-inflammatory / anti-fibrotic actions (NFkB)

Trivedi et al. Exp. Rev. Clin. Pharm. 2016

Integrin αVβ6 expression in murine sclerosing cholangitis



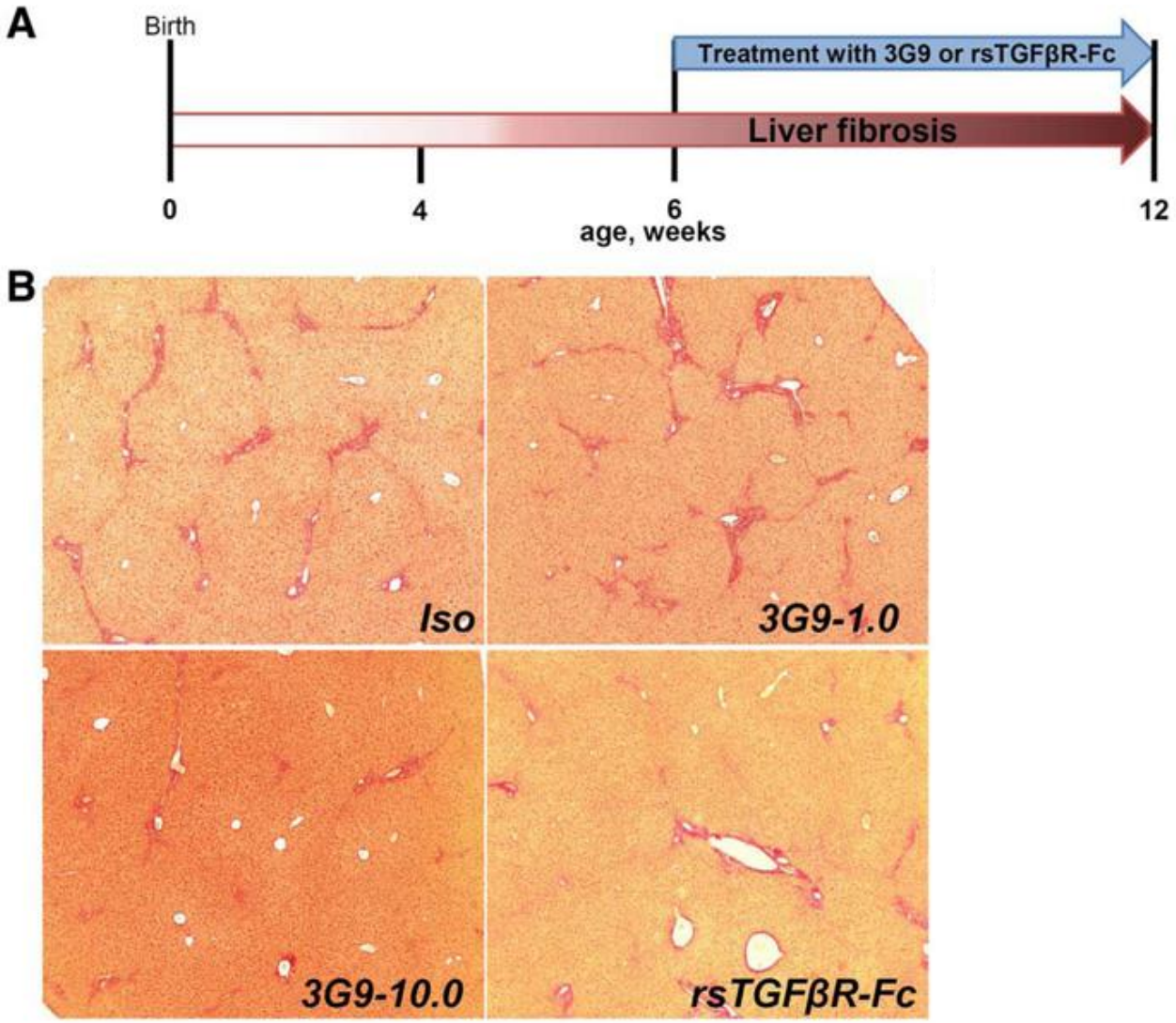
Periductal fibrosis; Sirius red



αVβ6 expressing cholangiocytes

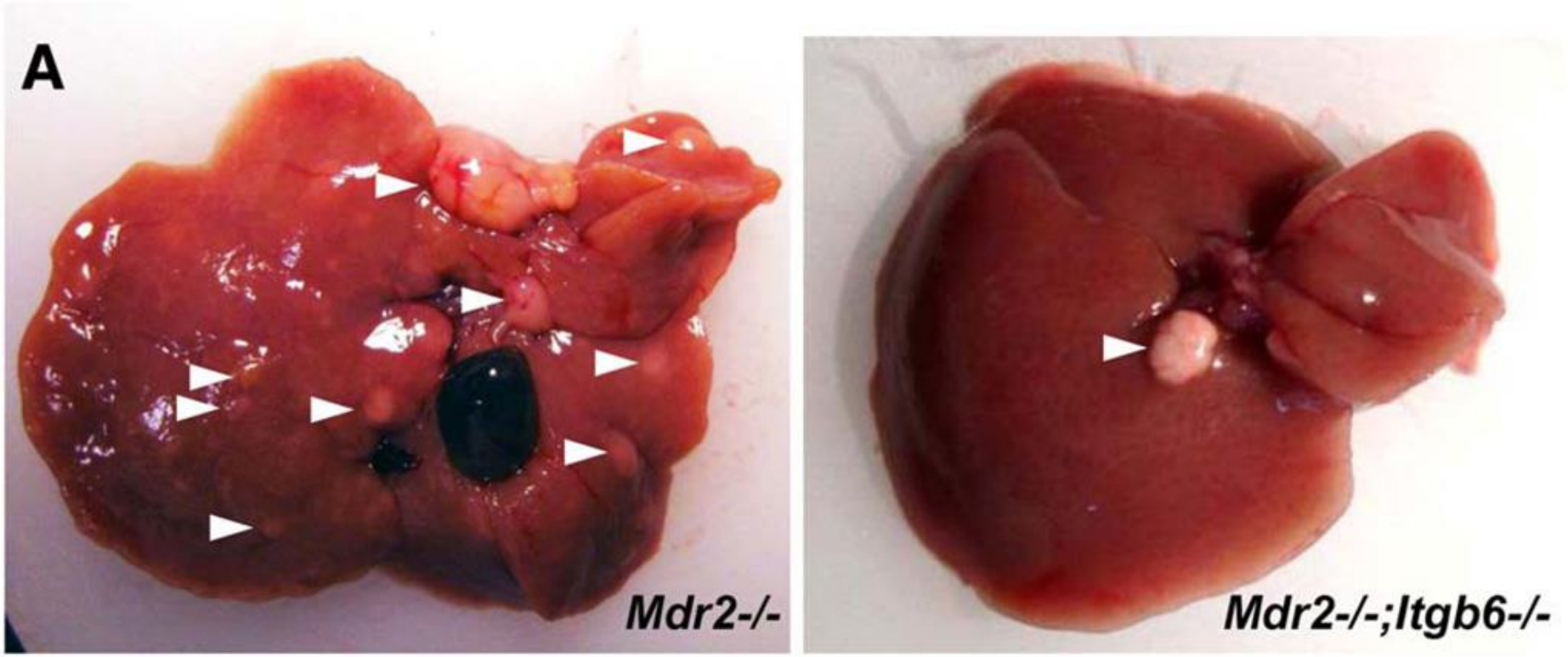
Peng et al. Hepatology. 2016

Integrin αVβ6 inhibition attenuates sclerosing cholangitis in mice



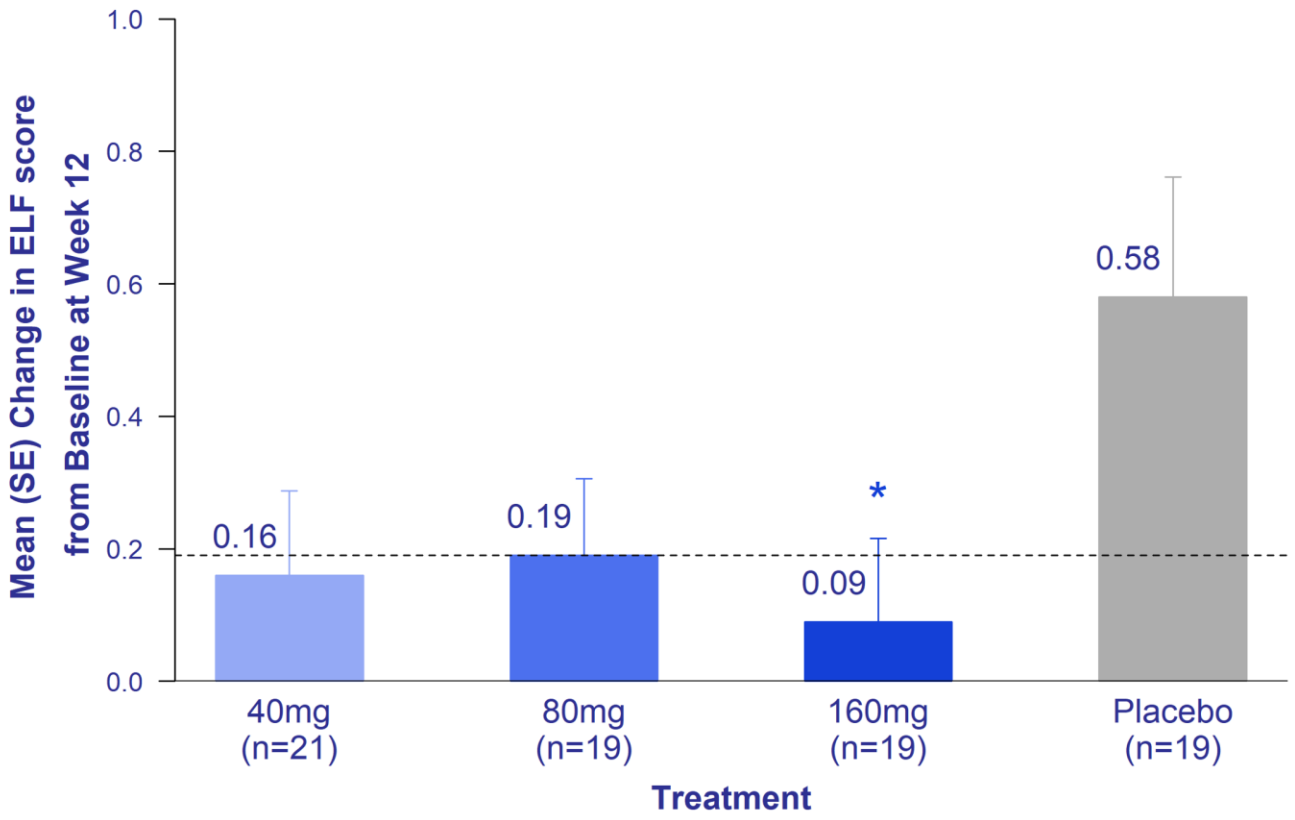
Peng et al. Hepatology. 2016

Targeted deletion of β6 prevents hepatobiliary carcinogenesis



Peng et al. Hepatology. 2016

INTEGRIS: Phase 2 dose finding study of anti avB6 / B1 in PSC



ELF score change ≥ 0.19 at 12 weeks shown to be predictive of clinical progression within 2 years[1]

* $p < 0.05$ vs placebo

Hirschfield, Trivedi et al. (ubpublished – data from Pliant press release)

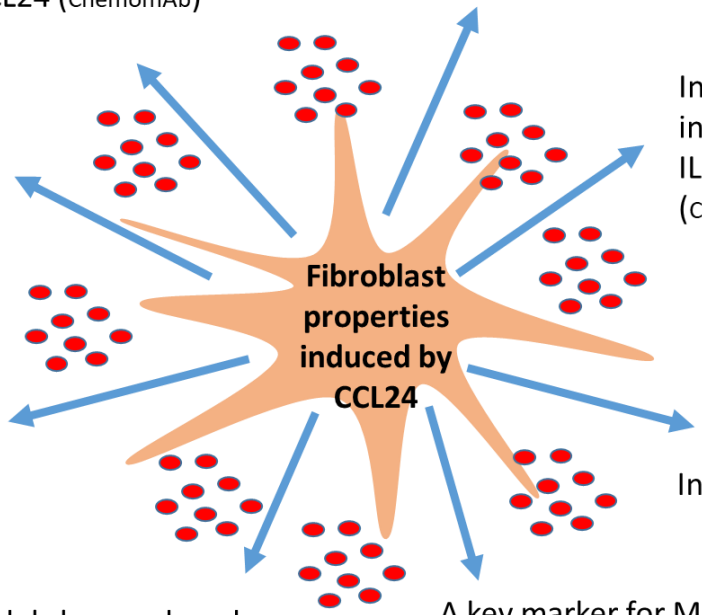
CCL24-CCR3 Axis Involvement in Human Fibroblasts

Transition to myofibroblasts
Induced alpha SMA expression in liver fibroblasts following Incubation with CCL24 (ChemomAb)

Induced secretion of pro fibrotic markers from liver fibroblasts :EGF, MMP9, MMP13, TIMP1 (ChemomAb)

Induced migration of fibrocytes (Isgro et al 2012)

Induced secretion of fibrosis associated inflammatory markers from liver fibroblasts: IL-1β, MIP-1α, Oncostatin, IFN-γ, VEGF, Leptin (ChemomAb)



Induced proliferation of lung fibroblasts (Kohan et al, 2010)

Induced collagen secretion from lung and liver fibroblasts (ChemomAb, Kohan et al, 2010)

Induced migration of dermal fibroblasts (ChemomAb)

Induced motility of hepatic stellate cells (ChemomAb)

CCL24 Knockout NASH model show reduced collagen deposition in the liver (ChemomAb)

A key marker for M2 macrophages supporting fibrosis (Braga et al 2015)

CCL24

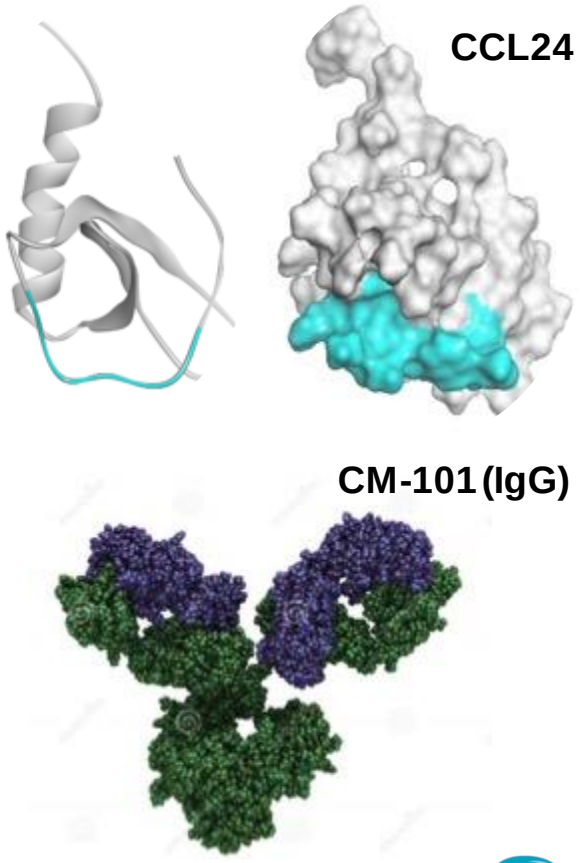
Confidential and Proprietary

ChemomAb

CM-101 is IgG1 Humanized Monoclonal Antibody Targeting CCL24

- CM-101's epitope identified, lead clone selected based on affinity and potency
- Fully humanized antibody
- Low manufacturing risk: expressed in CHO cells; GMP batches completed
- Typical PK profile for an IgG1 antibody
- Pre-clinically tractable: high cross reactivity with murine, rat and monkey CCL24
- Easy target engagement tracking using a validated method for measurement of total serum CCL24
- Available in both IV and SC formulations

Three dimensional structure of CCL24 and CM-101 (IgG)



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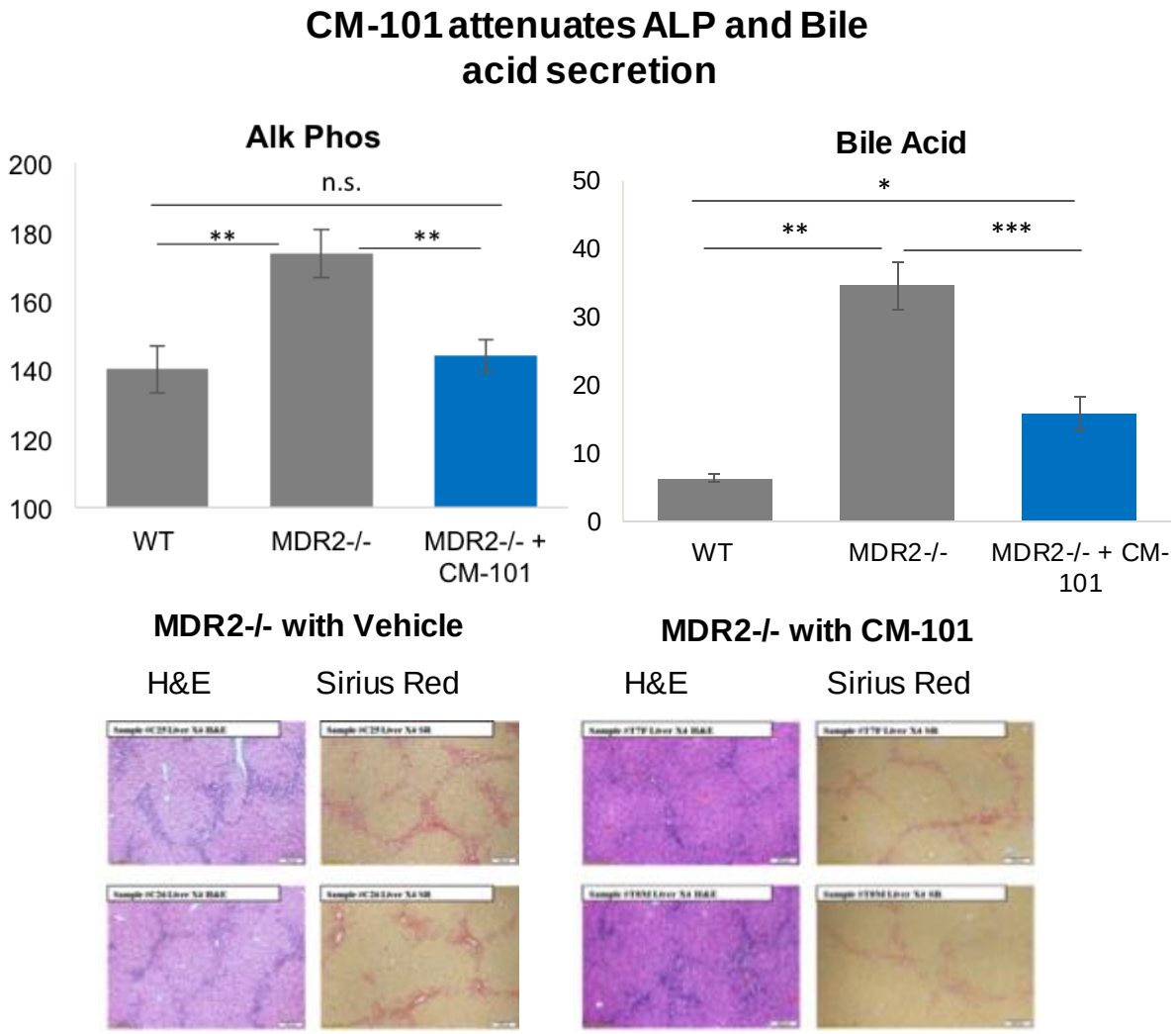
ChemomAb

CM-101 Reduces Liver Collagen and ALP in Experimental PSC Models (MDR2-/- Knockout Mice)



***p≤0.001; **p ≤0.01; *p ≤0.05

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