Lille 2 Université du Droit et de la Santé

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Auto-immune liver diseases: treatment of difficult patients

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MIVB-H
CENTRE DE RÉFÉRENCE
MALADIES INFLAMMATOIRES
DES VOIES BILIAIRES ET
HÉPATITES AUTO-IMMUNES

Clinical case n°3

Clinical vignette

- 39 YO woman
- No significant past medical history except sicca complex for 2 years
- No medication ongoing
- Has smoked 15 cig/day for 20 years
- Asymptomatic except dry eyes and mouth
- Referred for the following abnormal liver tests:
  - AST 1.2N, ALT 1.5N
  - GGT 6N, ALP 3N
  - Bilirubin normal

Clinical vignette

- AMA negative
- ANA positive 1/160 (specificity and pattern not determined)
- IgG et IgA normal
- IgM 2.70 g/l
- Total cholesterol 2.50 g/l

Questions

- Are ANA + cholestasis sufficient to confirm the diagnosis of PBC?
- In order to confirm the diagnosis of PBC, do you recommend further characterization of ANA?

AMA in PBC

- Present in 95% of PBC (vs. 0.5% in general population)
- Present in 10-20% of cases of AIH (overlap syndrome?)

Autoantigens and primary biliary cirrhosis (adapted from reference [67]).

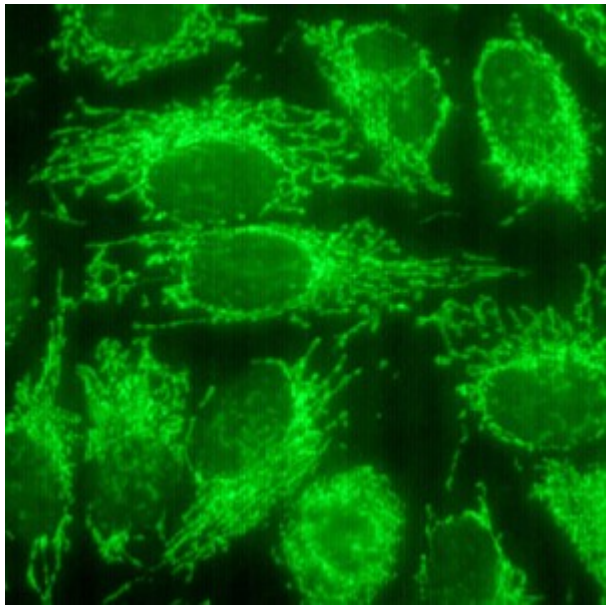
	Autoantigens	
Mitochondrial antigens	E2 subunits of 2-OADC	PDC-E2
		OGDC-E2
		BCOADC-E2
	Pyruvate dehydrogenase complex	E3BP PDC E1α
Nuclear antigens	Nuclear pore complex	gp210
		nucleoporin 62
	Multiple nuclear dots	Sp100
		PML
	Anticentromere	

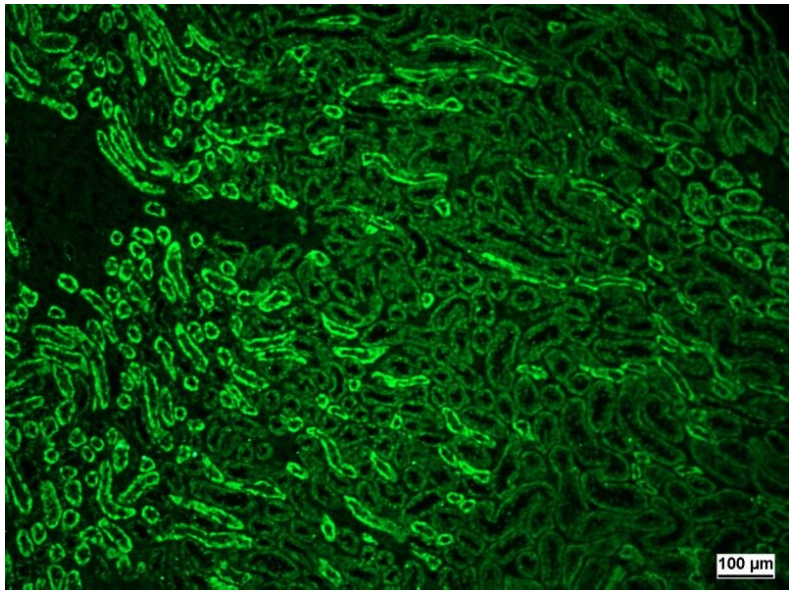
2-OADC: 2-oxo-acid dehydrogenase complex; PDC: Pyruvate dehydrogenase complex; OGDC: Oxoglutarate dehydrogenase complex; BCOADC: Branched chain 2-oxo-acid dehydrogenase complex; E3BP: Dihydrolipoamide dehydrogenase (E3)-binding protein; gp210: Nuclear pore glycoprotein-210; sp100: nuclear body speckled 100 kDa; PML: promyelocytic leukemia.

Hirschfield Best Pract Res Clin Gastroenterol 2011

AMA

- Considered positive if ≥1:40
- Detected by immunofluorescence, confirmation by WB or ELISA
- Are not specific of an organ





Other antibodies

Anti-nuclear antibodies and PBC (adapted from ref [49]).

	Prevalence in AMA positive PBC (%)	Prevalence in AMA negative PBC (%)	Specificity for PBC diagnosis (%)	Sensitivity for PBC diagnosis (%)
ANA positive[a]	47–48	68–85	Very low	Very low
MND[a]	12–24	38–41	Unknown	Unknown
RLM[a]	6–14	31–50	Unknown	Unknown
Speckled	24	41–46	Unknown	Unknown
Anti-centromere	14–20	14–23	Unknown	Unknown
Anti-Sp100	24–31	38–54	97	30
Anti-gp210	16–18	15–45	99	10–25

[a] Significant differences in the prevalence of ANA, multiple nuclear dot-like and perinuclear/rim-like membranous antibodies between AMA-positive and AMA-negative PBC.

Nuclear dots and perinuclear rims suggestive of PBC-associated ANA

Using immunofluorescence:

- Nuclear dots suggestive of anti-Sp100 Ab,
- Perinuclear rims suggestive of anti-gp210 Ab

Specificity confirmed by specific ELISA assays

Hirschfield Best Pract Res Clin Gastroenterol 2011

Diagnosis of PBC

Recommendations

7. EASL recommends that in adult patients with cholestasis and no likelihood of systemic disease, a diagnosis of PBC can be made based on elevated ALP and the presence of AMA at a titre >1:40 (**III**, **1**).
8. EASL recommends that in the correct context, a diagnosis of AMA negative PBC can be made in patients with cholestasis and specific ANA immunofluorescence (nuclear dots or perinuclear rims) or ELISA results (sp100, gp210) (**III**, **1**).
9. EASL recommends against liver biopsy for the diagnosis of PBC, unless PBC-specific antibodies are absent, coexistent AIH or NASH is suspected, or other (usually systemic) co-morbidities are present (**III**, **1**).
10. AMA reactivity alone is not sufficient to diagnose PBC. EASL recommends following-up patients with normal serum liver tests who are AMA positive with annual biochemical reassessment for the presence of liver disease (**III**, **1**).

- If AMA-, ANA required for the diagnosis of PBC
- ANA also helps predict patient outcome
- Liver biopsy only required if AMA/ANA negative and/or overlap suspected
- In case of AMA+ without cholestasis, assessment of ALP every year required

EASL J Hepatol 2017

Investigations in PBC: summary

Table 4. Overview of utility of investigations in PBC.

Test	Finding	Suspicion	Diagnosis	Prognosis	Notes
ALP	↑	✓	✓	✓	Values associated with disease progression
AST/ALT	↑	✓		✓	Prominent elevation may be suggestive of PBC with features of AIH
GGT	↑	✓			Reflects cholestatic liver injury
IgM	↑	✓			Elevated values associated with disease
AMA (>1/40)	+		✓		Diagnostic hallmark in over the 90% of patients in correct clinical context
Specific ANA	+		✓		Specific immunofluorescence patterns: Perinuclear rims, nuclear dot, centromere; present in 30%
anti-gp210	+		✓	✓	Specific immunoassays available
anti-sp100	+		✓		Specific immunoassays available
anti-centromere	+			✓	Associated with portal hypertensive phenotype
Bilirubin	↑			✓	Elevation at late stages; frequently indicative of cirrhosis except in patients with ductopenic non-cirrhotic variant
Platelets	↓			✓	Indicative of cirrhosis
INR	↑			✓	Indicative of cirrhosis
Albumin	↓			✓	Indicative of cirrhosis

ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase; IgM, immunoglobulin M; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; INR, international normalised ratio.

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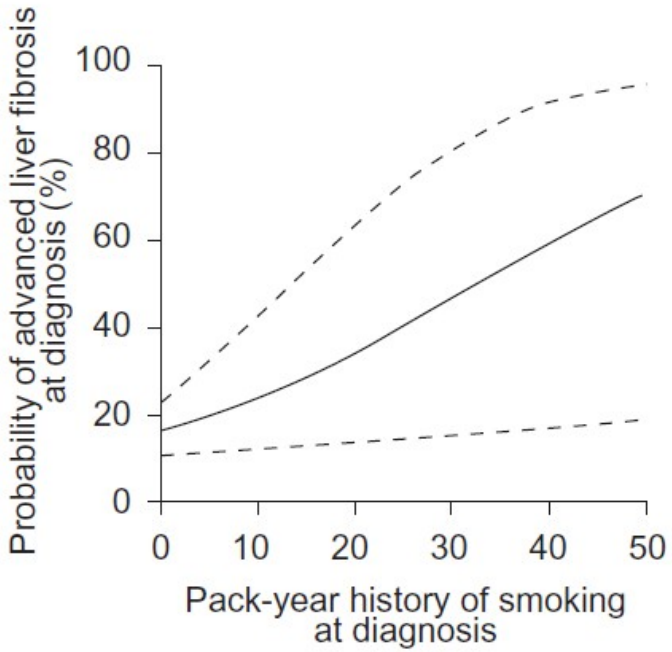
Questions

- Diagnosis of PBC confirmed with anti-gp210 Ab >1/160
- Do you recommend tobacco cessation?
- Is bone mineral density assessment required?
- Do you perform liver biopsy to assess liver fibrosis?

Role of smoking



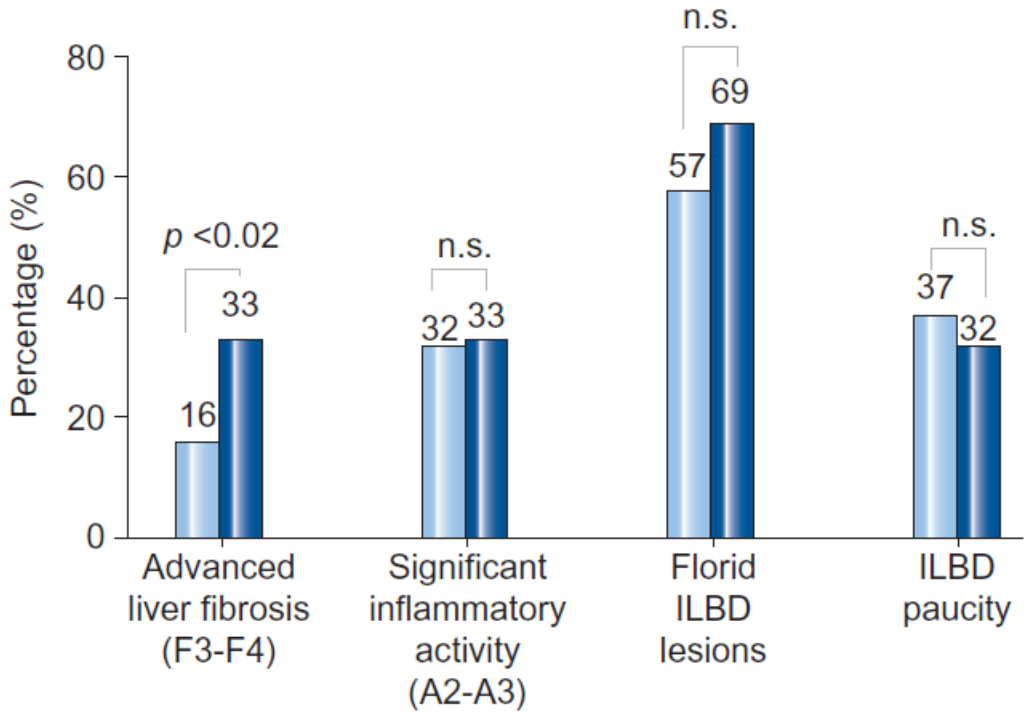


Fig. 1. Distribution of elementary histological lesions at presentation according to smoking history.

Corpechot et al. J Hepatol 2012

Osteoporosis and PBC

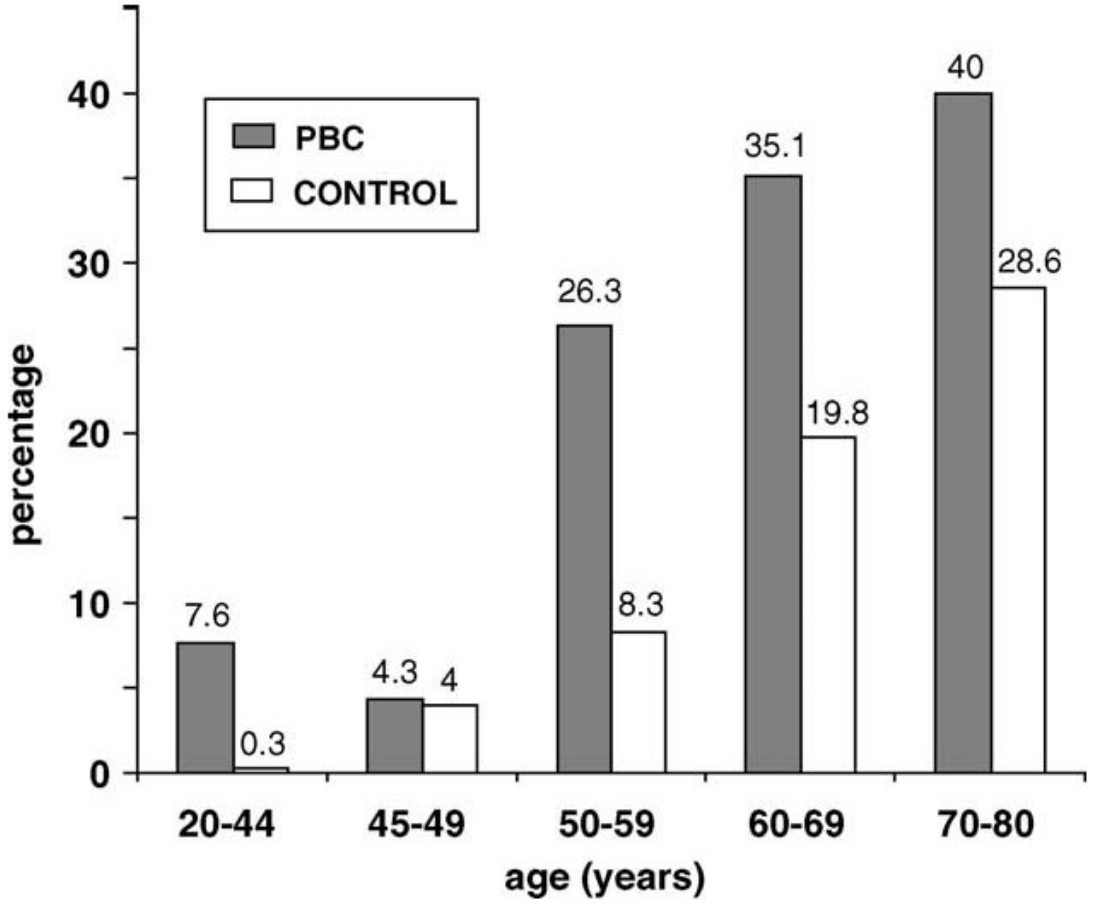


Fig. 1. Prevalence of osteoporosis in patients with primary biliary cirrhosis (closed bars) and controls (empty bars) according to ranges of age.

142 women with PBC with matching according to osteoporosis

Guanabens et al. J Hepatol 2005

Osteoporosis and PBC

Table 1
Clinical and laboratory data of patients with and without osteoporosis

	Osteo-porosis	No osteo porosis	*P*
Age (years)	60.2±1.2	51.5±0.9	0.000
Menopause (%)	91.3	58.3	0.000
Body mass index (kg/m^2)	24.5±0.5	26.1±0.4	0.026
Duration of PBC (years)	4.2±0.6	2.4±0.3	0.004
Duration of menopause (years)	13.8±1.3	8.2±0.9	0.000
Bilirubin (mg/dl)	2.0±0.4	1.4±0.3	0.003[a]
Alkaline Phosphatase (u/l)	947±125	634±48	0.005
γ-glutamyl transferase (u/l)	274±38	230±23	n.s.
Asparate amino transferase (u/l)	98±14	79±7	n.s.
Albumin (g/l)	40.0±0.6	42.4±0.4	0.001
Prothrombin index (%)	93.4±1.9	98.5±0.4	0.000
Mayo risk score	5.15±0.11	4.26±0.08	0.000
Histological stage III and IV (%)	50	15	0.001

[a] After Ln transformation.

142 women with PBC with matching according to osteoporosis

Guanabens et al. J Hepatol 2005

Osteoporosis and PBC

Table 2. Clinical Features, Densitometric Data, and Fractures in Patients With PBC According to Osteoporosis

	Osteoporosis at lumbar spine			Osteoporosis at femoral neck		
	Yes	No	*P* value	Yes	No	*P* value
No.	55	123		19	119	
Age (*y*)	60.7 ± 1.1	53.4 ± 0.9	<.001	64.9 ± 2.1	55.0 ± 0.9	<.001
Menopause (%)	96.4	76	.001	94.7	85.2	NS
Height (*cm*)	154.0 ± 0.7	157.8 ± 0.5	<.001	154.6 ± 1.4	157.2 ± 0.5	NS
Weight (*kg*)	58.7 ± 1.1	65.0 ± 0.9	<.001	60.5 ± 1.8	64.6 ± 0.9	NS
BMI (kg/m^2)	24.7 ± 0.4	26.1 ± 0.4	.025	25.4 ± 0.8	26.1 ± 0.4	NS
Duration PBC (*y*)	4.4 ± 0.6	2.7 ± 0.3	.002	5.4 ± 1.3	2.7 ± 0.3	.002
Bilirubin (*mg/dL*)	1.7 ± 0.3	1.2 ± 0.2	.007[a]	1.1 ± 0.2	0.8 ± 0.1	.07[a]
AP (*u/L*)	824 ± 108	559 ± 40	.005	461 ± 63	484 ± 35	NS
gGT (*u/L*)	234 ± 33	194 ± 19	NS	153 ± 32	157 ± 17	NS
ALT (*u/L*)	86 ± 12	68 ± 6	NS	60 ± 10	61 ± 6	NS
Albumin (*g/L*)	41.3 ± 0.5	42.9 ± 0.4	.017	40.4 ± 0.9	42.4 ± 0.3	.019
Prothrombin index (%)	94.4 ± 1.7	98.6 ± 0.3	.001	98.4 ± 0.7	98.1 ± 0.4	NS
Histological stage	2.31 ± 0.16	1.64 ± 0.07	<.001	2.1 ± 0.25	1.7 ± 0.08	.06
Stages I and II (%)	25 (52.1)	103 (85.8)	<.001	11 (61.1)	97 (82.9)	.03
Lumbar BMD						
L2–L4 (g/cm^2)	0.807 ± 0.010	1.080 ± 0.011	<.001	0.798 ± 0.030	1.043 ± 0.014	<.001
T score	−3.23 ± 0.08	−0.95 ± 0.09	<.001	−3.30 ± 0.24	−1.28 ± 0.14	<.001
Z score	−1.60 ± 0.09	0.06 ± 0.07	<.001	−1.53 ± 0.20	−0.18 ± 0.19	<.001
Femoral BMD						
Neck (g/cm^2)	0.686 ± 0.013	0.842 ± 0.012	<.001	0.636 ± 0.009	0.835 ± 0.011	<.001
T score	−2.28 ± 0.10	−1.12 ± 0.08	<.001	−2.84 ± 0.07	−1.20 ± 0.07	<.001
Z score	−0.97 ± 0.12	−0.33 ± 0.08	<.001	−1.39 ± 0.10	−0.35 ± 0.07	<.001
Overall fractures (%)	30	15.8	.035	61.1	16.1	<.001
Vertebral (%)	22	6.8	.005	38.8	6.9	<.001
Non-vertebral (%)	16	9.2	NS	38.8	9.3	.001

185 PBC patients

Guanabens et al. Gastroenterology 2010

Osteoporosis and PBC

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Bilirut						.07[a]
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Albur						.019
Prothr						NS
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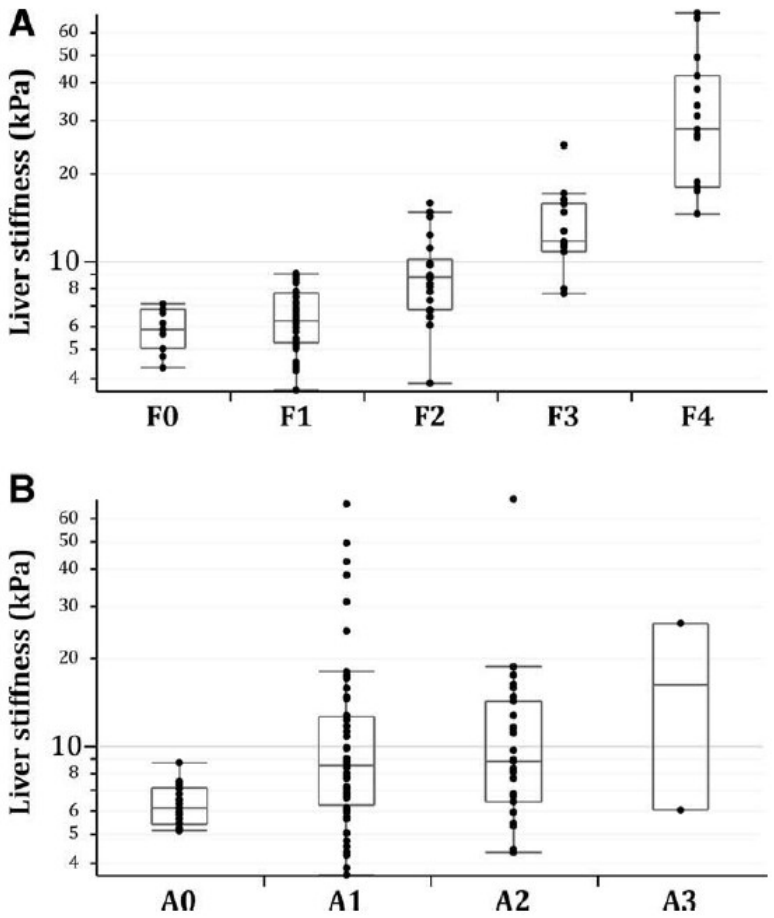
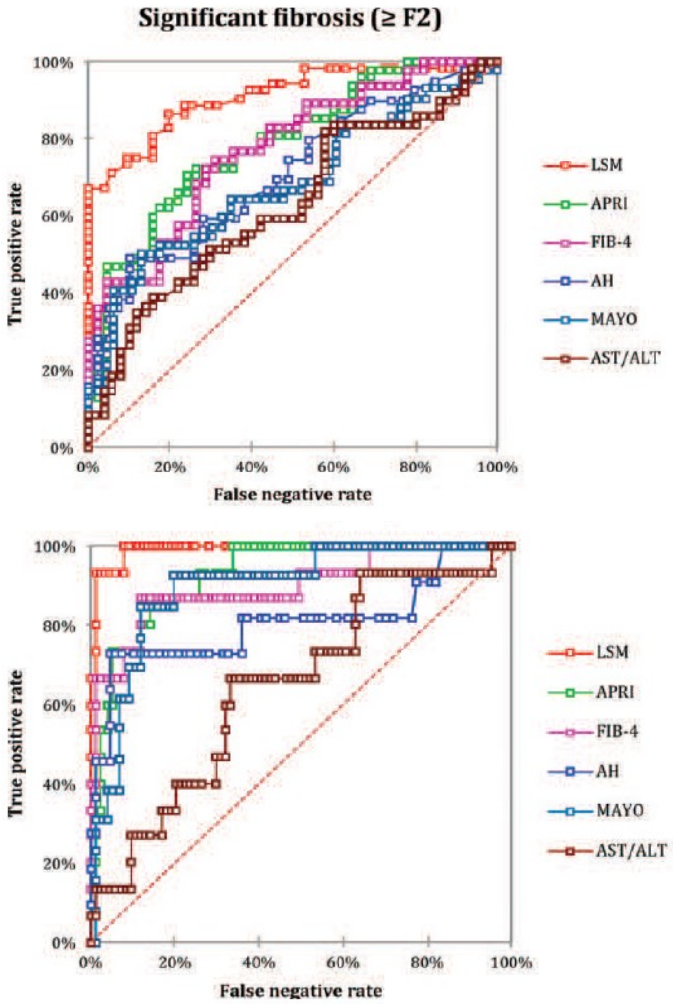
EASL recommends bone mineral density assessment at baseline and 1-5 years thereafter according to baseline results and general risk factors of osteoporosis

185 PBC patients

Guanabens et al. Gastroenterology 2010

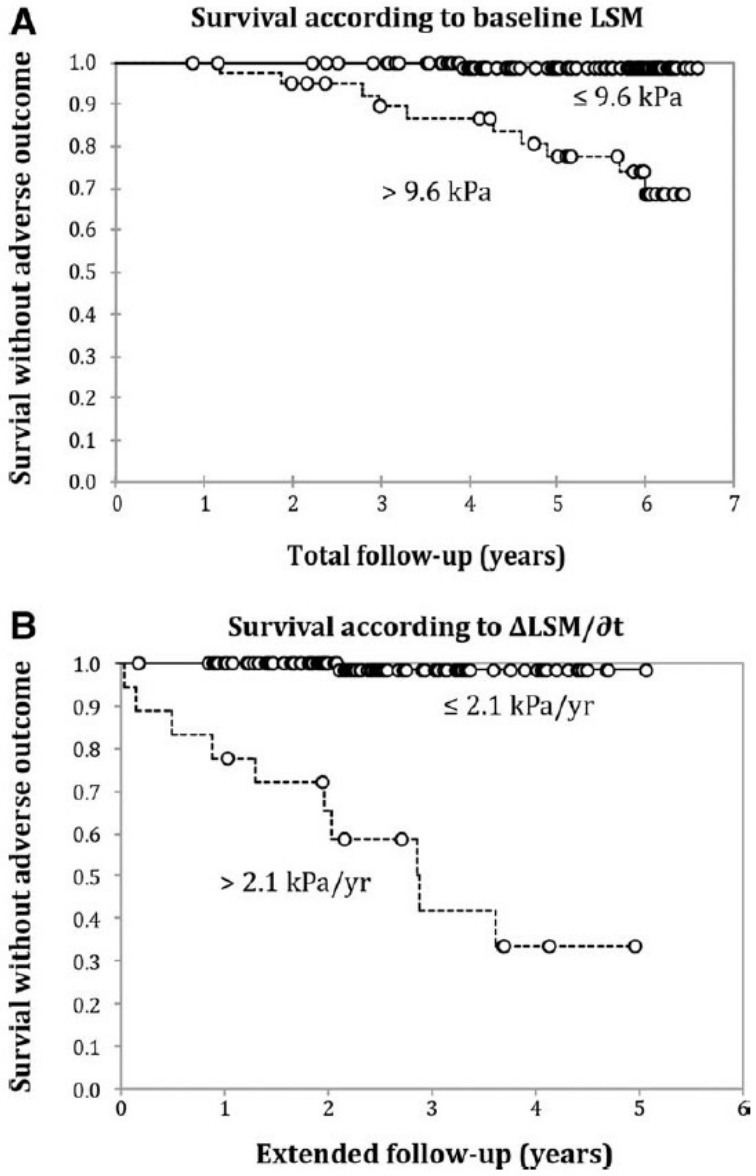
Fibrosis assessment





Corpechot et al. Hepatology 2012

Fibrosis assessment

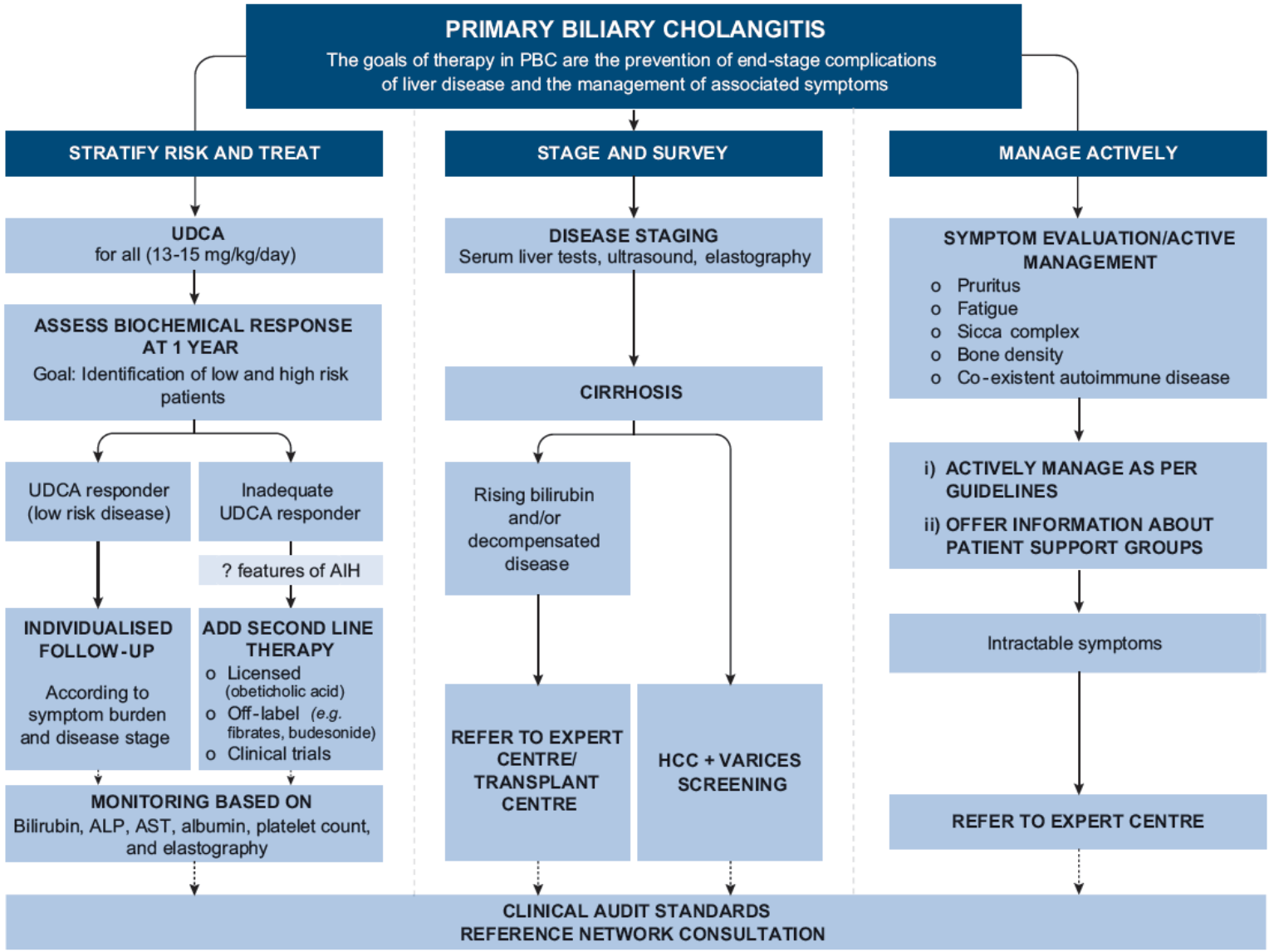


Stage	No.	Cutoff
Diagnostic cohort		
≥F1	92	7.1
≥F2	52	8.8
≥F3	30	10.7
=F4	15	16.9
Bootstrap statistic		
≥F1	9,219	7.1 ± 0.3 (5.9-7.5)
≥F2	5,225	8.7 ± 0.9 (7.3-9.8)
≥F3	3,002	10.9 ± 0.8 (10.7-11.5)
=F4	1,492	16.1 ± 1.8 (14.4-17.8)

Three values to keep in mind:
9.6 kPa, 16.9 kPa (cirrhosis) and 2.1 kPa/year

Corpechot et al. Hepatology 2012

Management



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Clinical vignette

- UDCA is started at 1000 mg/day (body weight 71 kg)
- After 6 months of treatment:
  - AST 1.1N (baseline was 1.2N)
  - ALP 2.5N (baseline was 3N)
- Do you consider adding second treatment?

Assessment of treatment response

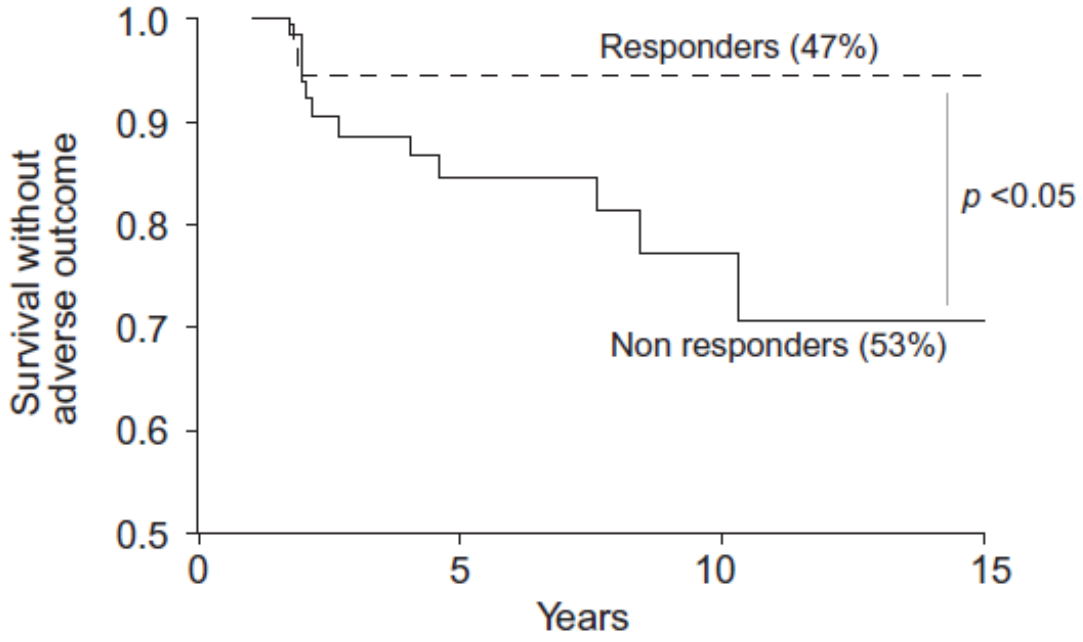

Fig. 3. Survival rates without adverse outcome in patients with early PBC, as defined by both normal bilirubin and albumin concentrations at baseline, according to the 1-year biochemical response to UDCA as defined by the Paris II criteria. The dotted curve represents survival of responders (n = 84). The solid curve represents survival of non-responders (n = 74).

Paris II criteria after 12 months of UDCA:

- ALP ≤ 1.5N
- AST ≤ 1.5N
- Bilirubine ≤ 1 mg/dl

Corpechot et al. Hepatology 2008
Corpechot et al. J Hepatol 2011

Assessment of treatment response

Table 5. Assessing response to UDCA therapy in PBC.

Qualitative binary definitions	**Time (months)**	**Treatment failure**
Rochester [101]	6	ALP ⩾2× ULN or Mayo score ⩾4.5
Barcelona [62]	12	Decrease in ALP ⩽40% and ALP ⩾1× ULN
Paris-I [63]	12	ALP ⩾3× ULN or AST⩾ 2× ULN or bilirubin >1 mg/dl
Rotterdam [102]	12	Bilirubin ⩾1× ULN and/or albumin <1× ULN
Toronto [98]	24	ALP >1.67× ULN
Paris-II [104]	12	ALP ⩾1.5× ULN or AST ⩾1.5× ULN or bilirubin >1 mg/dl
Ehime [103]	6	Decrease in GGT ⩽70% and GGT ⩾1× ULN
Continuous scoring systems	**Time (months)**	**Scoring parameters**
UK-PBC [107]	12	Bilirubin, ALP and AST (or ALT) at 12 mo. Albumin and platelet count at baseline
GLOBE [106]	12	Bilirubin, ALP, albumin, and platelet count at 12 mo. Age at baseline

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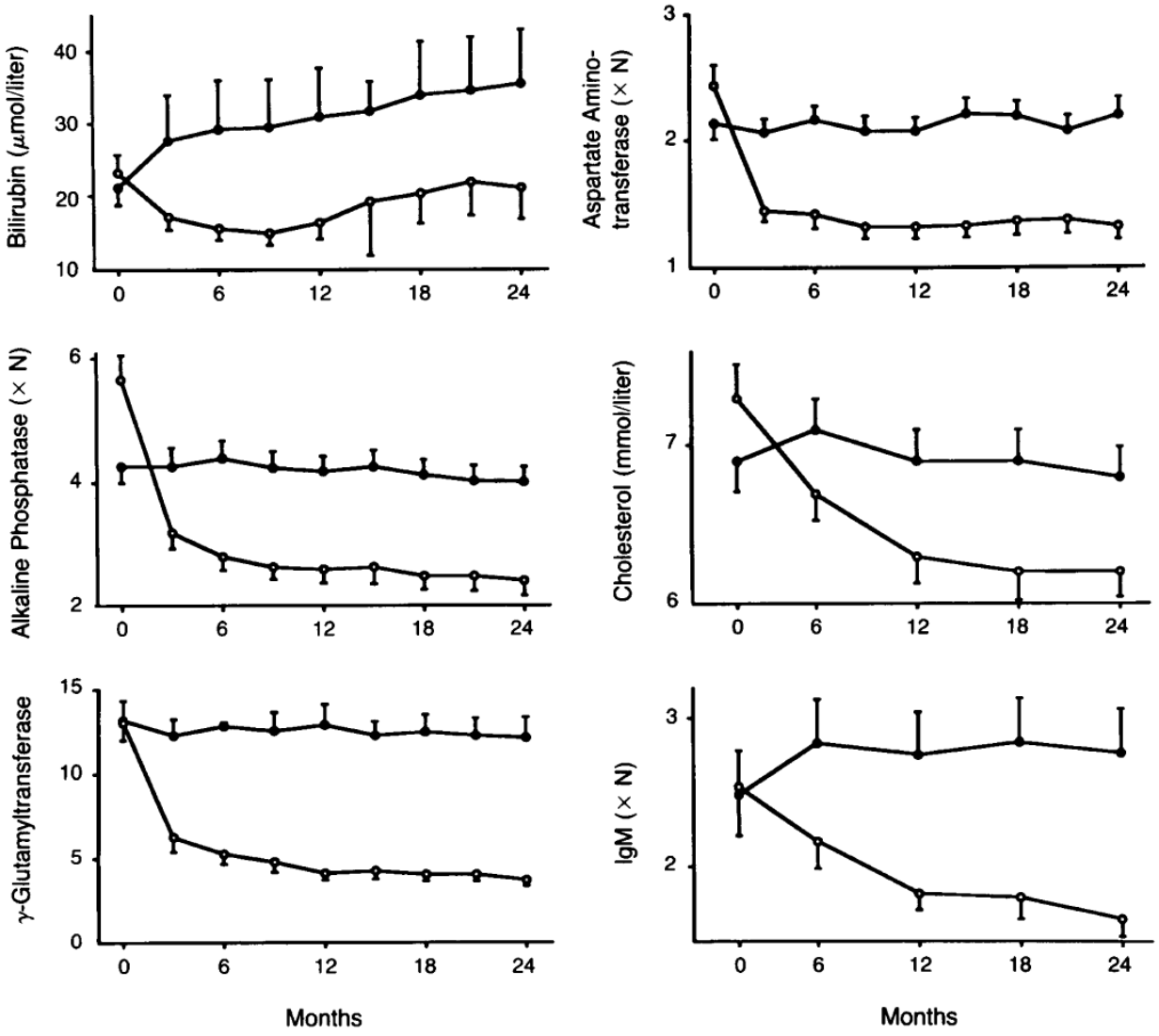
Biological response and UDCA



RCT of 146 patients with biopsy-proven PBC

73 patients treated with UDCA (open circles)
73 patients treated with placebo (solid circles)

Dose of UDCA 13-15 mg/kg/day

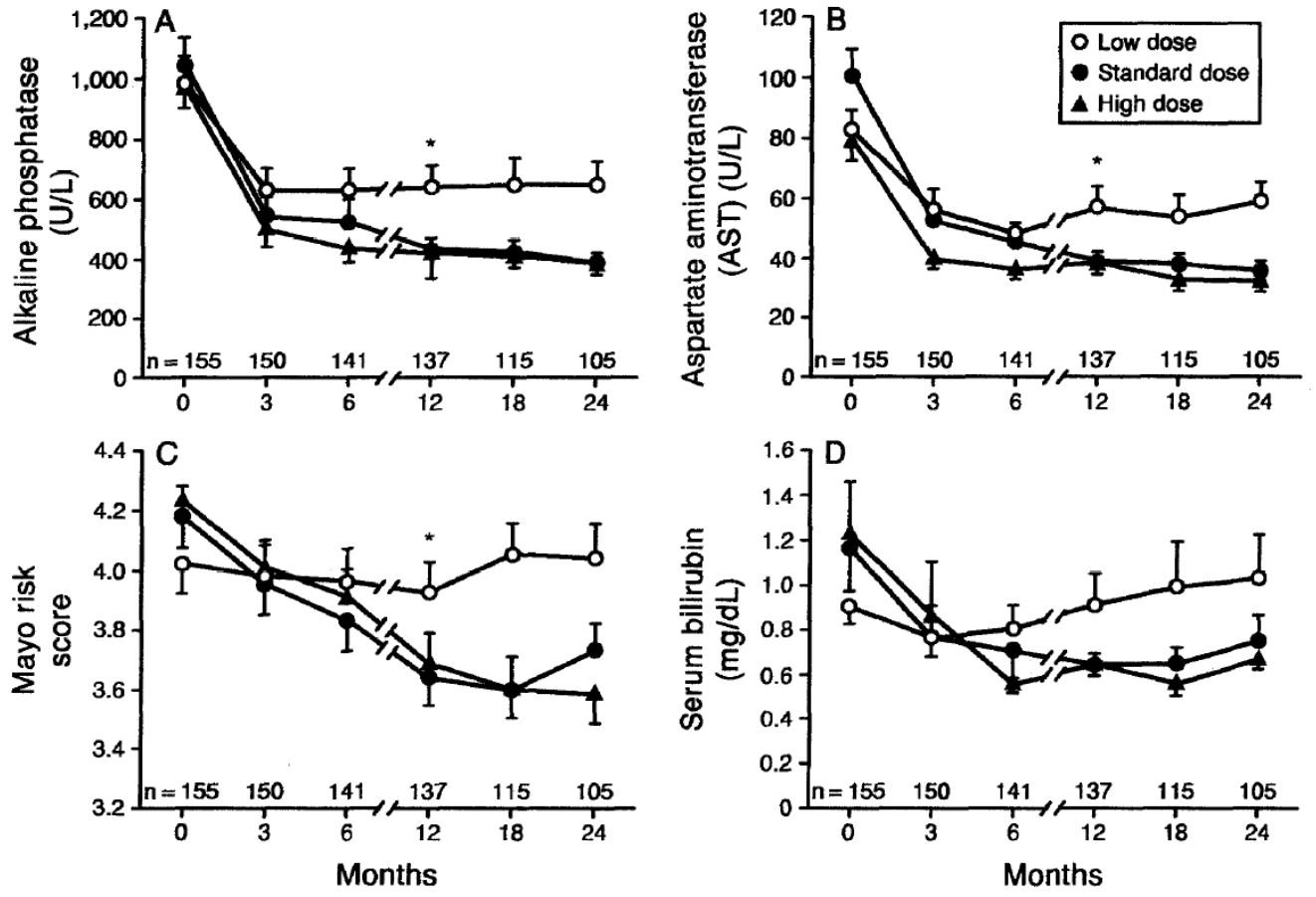
Most of biological effect seen at 6 months

Poupon et al. N Engl J Med 1991

Clinical vignette

- Liver tests remained stable after 12 months
- Additional treatment required:
  - Increased dose of UDCA?
  - Obeticholic acid?
  - Fibrate?

Dose of UDCA



Mayo model:

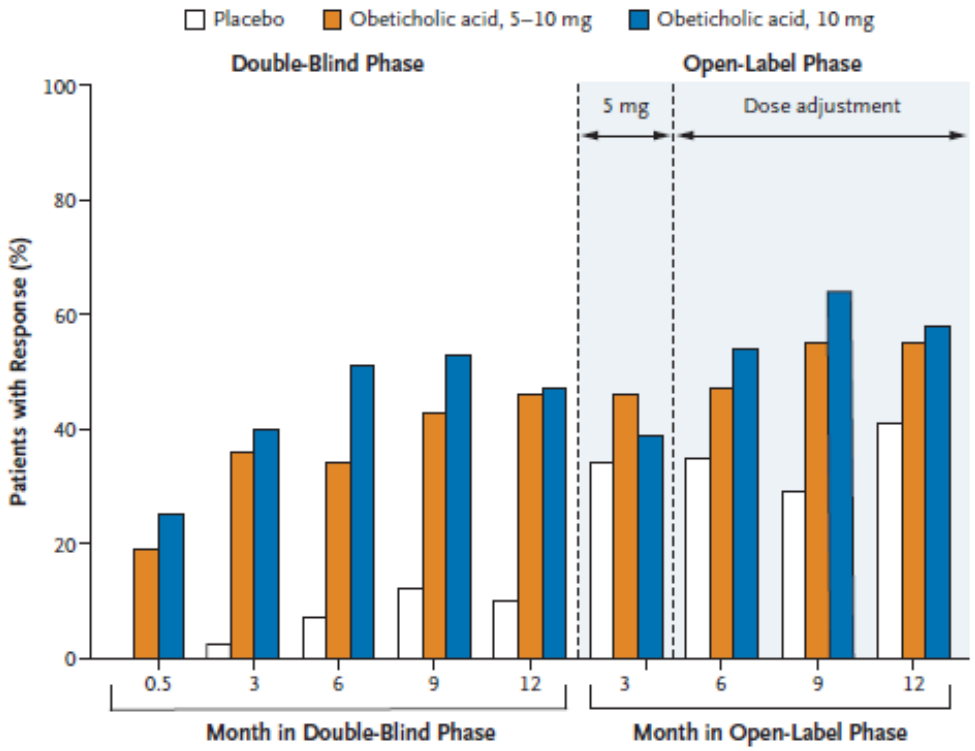
- Age
- Albumin
- Bilirubin
- Prothrombin time
- Edema or ascites

Angulo et al. J Hepatol 1999

Inadequate response to UDCA

- Can be observed if:
  - Inadequate dosing regimen
  - Compliance
  - Overlap syndrome
  - Thyroid disorders
  - Celiac disease
- Chromatography: exceptional cases, UDCA 50-80% of total bile acids

OCA in PBC: POISE study



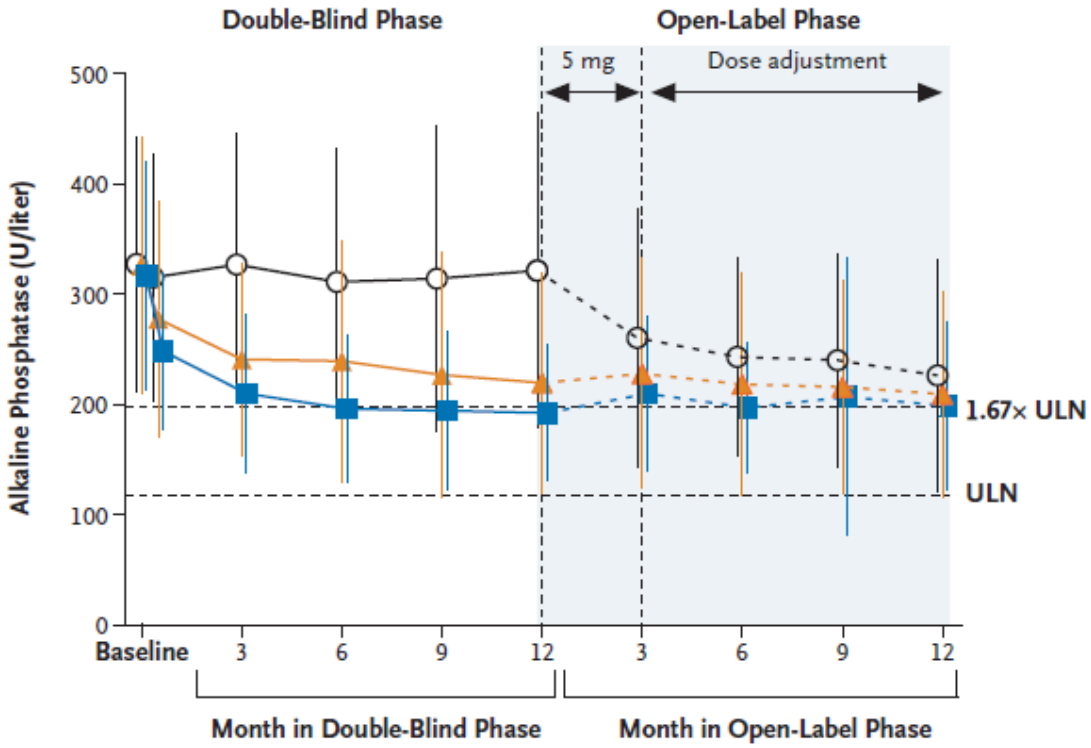
No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59

Phase III double blind RCT in NR to UDCA
Primary endpoint at 12 months:

- ALP ≤ 1.67xN and
- Decrease in ALP ≥15% and
- Bilirubin ≤N

Nevens et al. N Engl J Med 2016

OCA in PBC: POISE study



Secondary endpoint

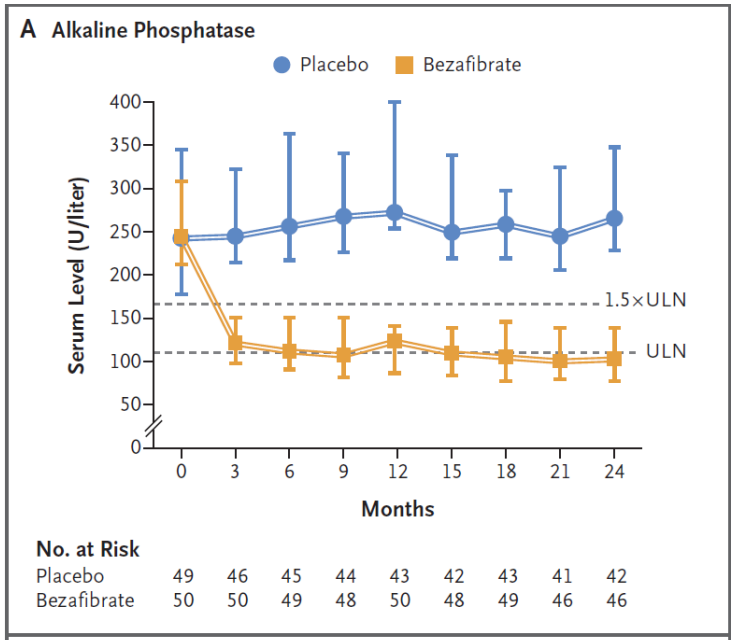
Table 2. Incidence of Adverse Events of 10% or More in any Treatment Group.*

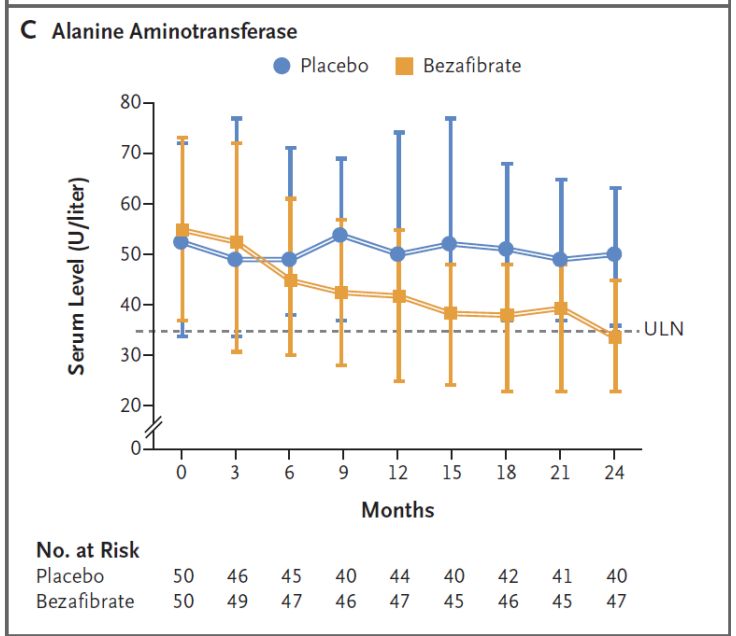
Event	Double-Blind Phase			Open-Label Extension
	Placebo (N=73)	Obeticholic Acid, 5–10 mg (N=70)	Obeticholic Acid, 10 mg (N=73)	Total Obeticholic Acid (N=193)
	number of patients (percent)			
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)
Nasopharyngitis	13 (18)	17 (24)	13 (18)	45 (23)
Headache	13 (18)	12 (17)	6 (8)	36 (19)
Fatigue	10 (14)	11 (16)	17 (23)	50 (26)
Nausea	9 (12)	4 (6)	8 (11)	28 (15)
Diarrhea	8 (11)	2 (3)	8 (11)	17 (9)
Back pain	8 (11)	4 (6)	4 (5)	24 (12)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)	20 (10)
Urinary tract infection	8 (11)	4 (6)	4 (5)	31 (16)
Dyspepsia	8 (11)	4 (6)	0	10 (5)
Arthralgia	3 (4)	4 (6)	7 (10)	32 (17)
Serious adverse event	3 (4)	11 (16)	8 (11)	27 (14)

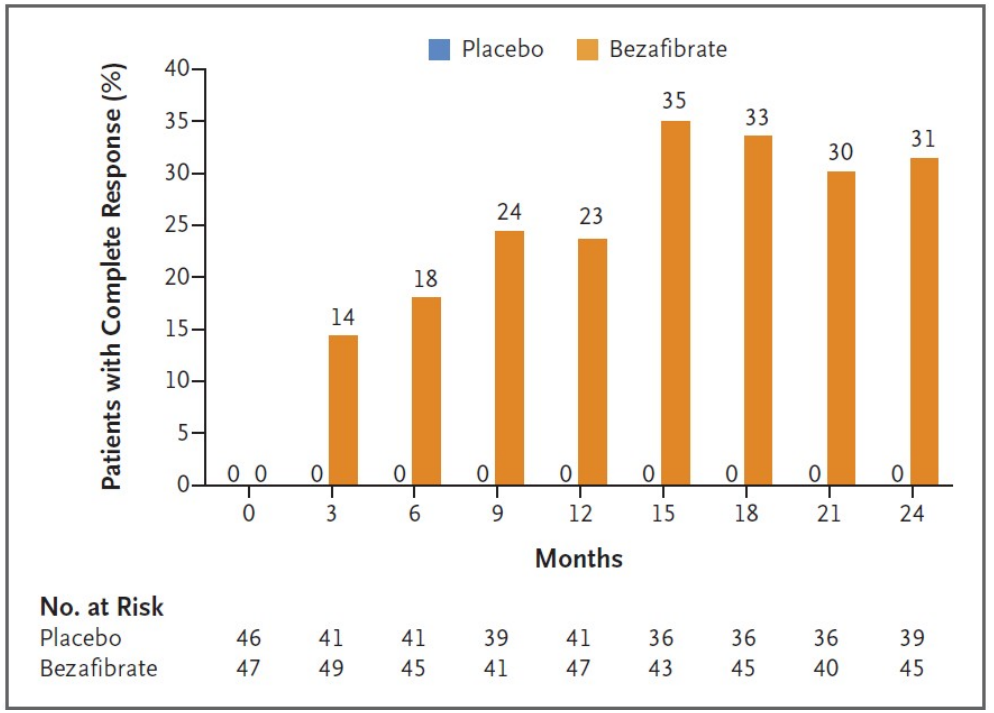
Tolerance

Nevens et al. N Engl J Med 2016

Bezafibrate in PBC







Patients intolérant or resistant to UDCA
(Paris II criteria assessed after at least 6 months)

Corpechot et al. N Engl J Med 2018

Bezafibrate in PBC

Table 3. Incidence of Adverse Events Occurring in 10% or More of Patients and All Serious Adverse Events.*

Event	Bezafibrate Group (N=50)	Placebo Group (N=50)
	no. of patients with event (%)	
Any adverse event	43 (86)	45 (90)
Arthralgia	7 (14)	11 (22)
Myalgia	10 (20)	5 (10)
Nasopharyngitis	9 (18)	10 (20)
Bronchitis	4 (8)	9 (18)
Depressive mood	7 (14)	8 (16)
Abdominal pain	7 (14)	6 (12)
Pruritus	4 (8)	7 (14)
Diarrhea	1 (2)	6 (12)
Flulike syndrome	5 (10)	5 (10)
Any serious adverse event	14 (28)	12 (24)
Aminotransferase level >5x ULN	3 (6)	1 (2)
Creatine kinase level >5x ULN	1 (2)	0
Creatinine increase with worsening stage of chronic kidney disease	1 (2)	0

Corpechot et al. N Engl J Med 2018

Clinical vignette

- ALP after 6 months of UDCA+OCA/bezafibrate are 1.4N and bilirubin is 1 mg/dl.
- Is treatment response sufficient?
- In case of inadequate response to OCA/bezafibrate, would you consider using triple therapy?

Triple therapy UDCA+OCA+bezafibrate

- 11 patients treated with UDCA + OCA (5 to 10 mg/day) for 5 years
- **Aim :** attempt to normalize ALP and bilirubin with the adjunction of bezafibrate (400 mg/day)

Patient characteristics

Mean age (years)	65
Female gender (%)	82
Pruritus	n = 8 (73 %) *
ALP (IU/l)	200
Total bilirubin (µmol/l)	11.6
Transient elastography (kPa)	9.3
Time of UDCA treatment (years)	6

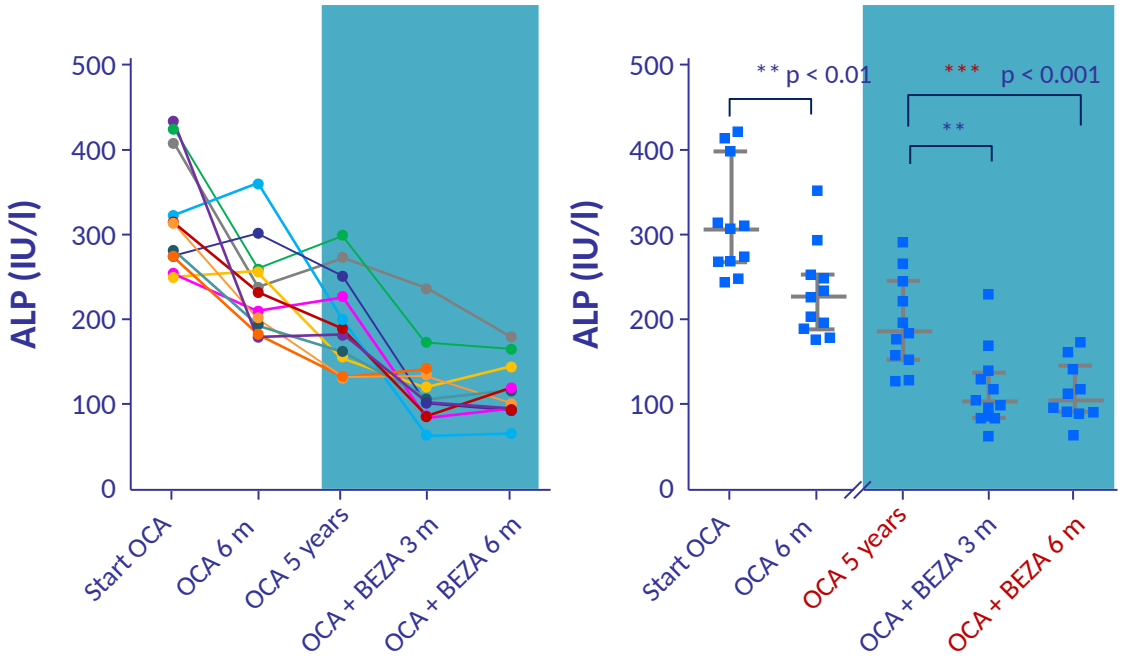
* Mean score for pruritus at 5.6

- Evaluation at 6 months in 10 patients – 1 had stopped bezafibrate because of myalgias
- Effect on pruritus :
  - Afters 6 months of triple therapy, pruritus had decreased in 5/8 patients (NS). Pruritus score had decreased from 5.6 to 4.4 points (p = 0.07)

Smets et al. EASL 2019, Abstr. LB-05

Triple therapy UDCA+OCA+bezafibrate

Evolution of ALP



Normal ALP : ≤ 105 IU/l (women) ; ≤ 130 IU/l (men)

- **UDCA + OCA (POISE)**
  - After 6 months : decrease in ALP in 73 % of patients
  - After 5 years : ALP abnormal in all patients
- **UDCA + OCA + BEZA**
  - After 6 months : decrease in ALP in all patients; p <

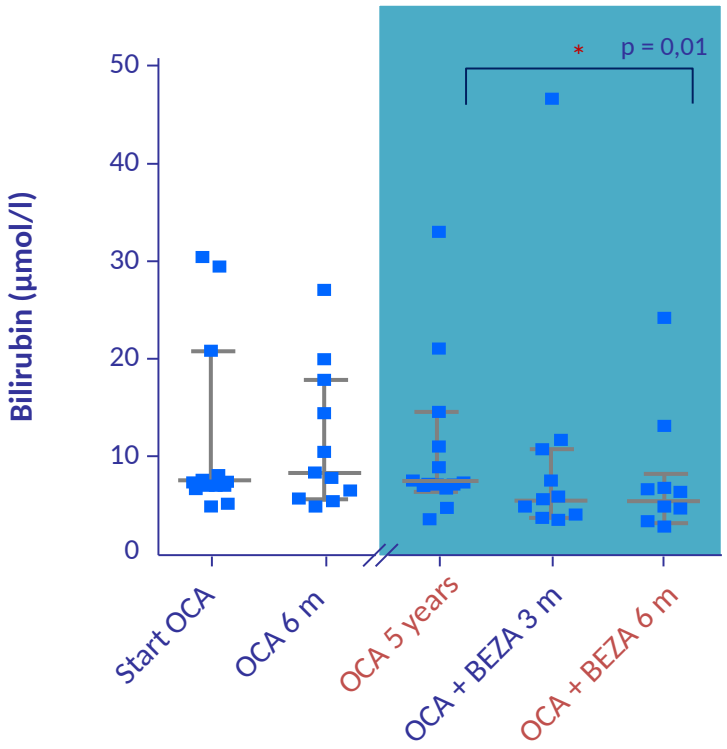
ALP normal in 5/10 patients

➔ **Normal level of ALP in 50 % of cases**

Smets et al. EASL 2019, Abstr. LB-05

Triple therapy UDCA+OCA+bezafibrate

Evolution of total bilirubin



- **UDCA + OCA (POISE)**
  - After 6 months : decrease in bilirubin in 64 % of patients
  - After 5 years : bilirubin **normal** in 9/11 patients (81 %)
- **UDCA + OCA + BEZA**
  - After 6 months : decrease in bilirubin in all patients ; p =

Bilirubin normal in 9/10 patients

➔ **Primary endpoint (normalization of ALP and bilirubin) reached in 50 % of cases**

Smets et al. EASL 2019, Abstr. LB-05

Triple therapy UDCA+OCA+bezafibrate (2)

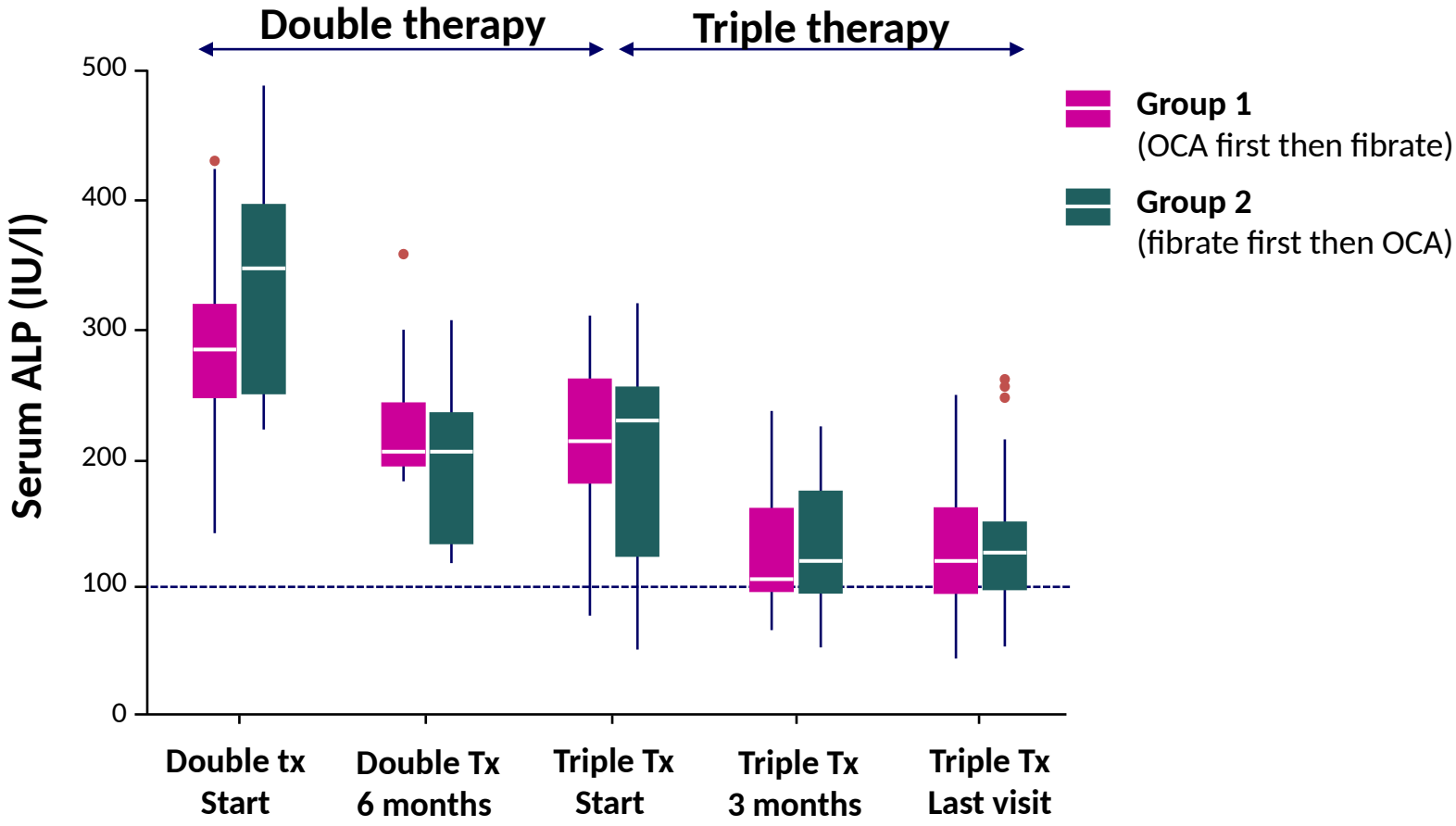
- Multicenter retrospective cohort
- Patients with PBC treated for at least 12 weeks with UDCA (13-15 mg/kg/d) + OCA (5-10 mg/j) + fibrates (bezafibrate 400 mg/d or fenofibrate 200 mg/d) because of an inadequate response to a second-line therapy (Paris 2 criteria)
  - Groupe 1 (n = 24) : OCA 2nd line and fibrate 3rd line
  - Groupe 2 (n = 26) : fibrate 2nd line and OCA 3rd line

Slope of decrease in ALP (primary endpoint)

Triple vs. Double therapy	Slope of decrease in ALP	SE	p
All patients	- 0.3085	0.0726	< 0.0001
Group 1	- 0.7960	0.1408	< 0.0001
Group 2	- 0.1825	0.0812	0.026

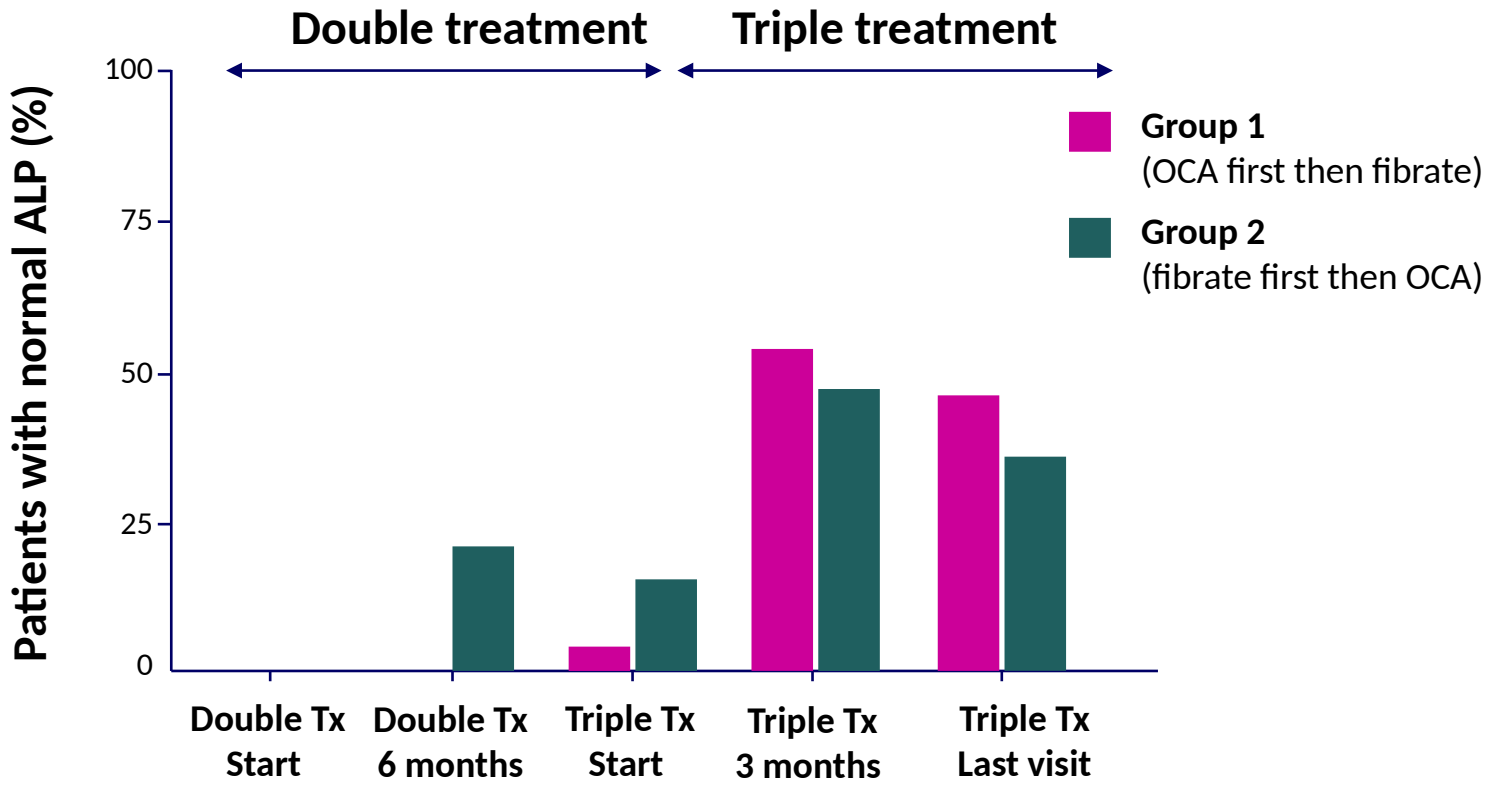
Soret et al. AASLD 2019, Abstr LP6

Triple therapy UDCA+OCA+bezafibrate (2)



Soret et al. AASLD 2019, Abstr LP6

Triple therapy UDCA+OCA+bezafibrate (2)

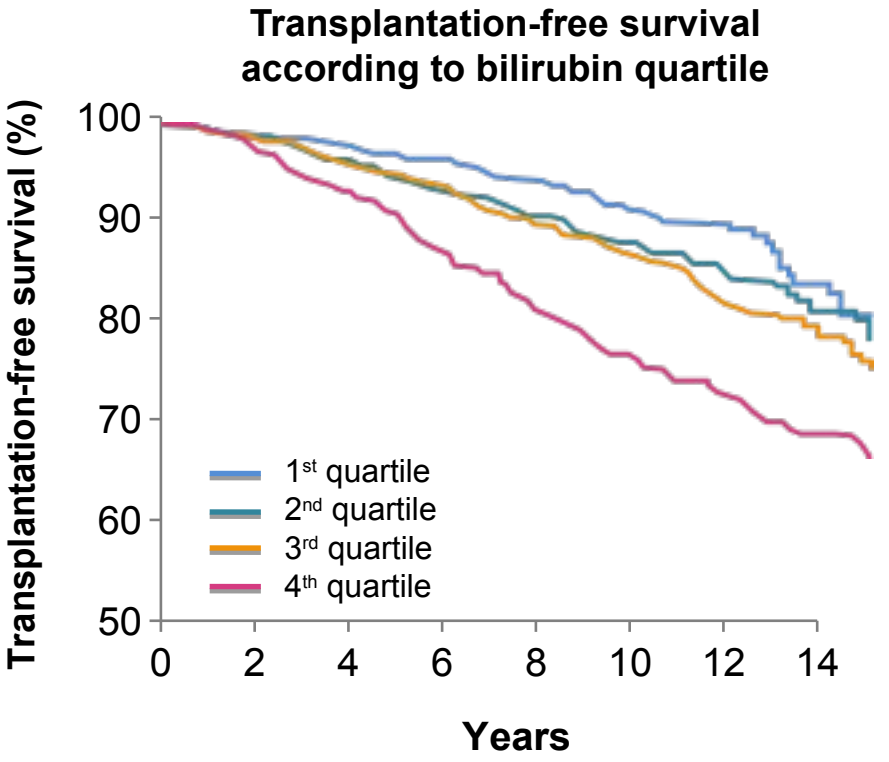


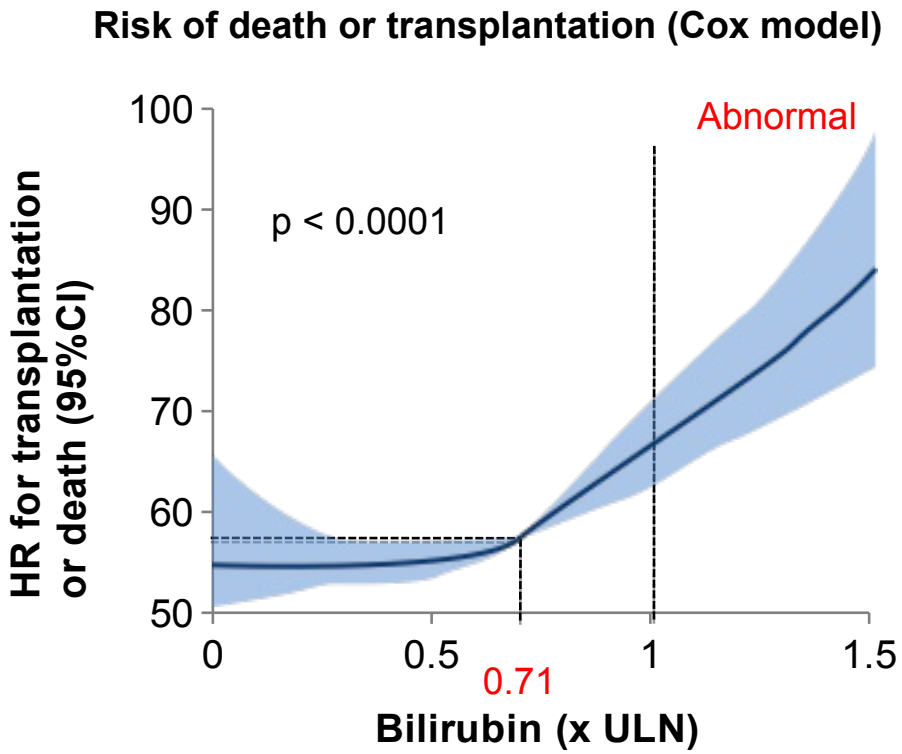
➔ **In patients with PBC and inadequate response to double therapy, triple treatment with UDCA+OCA+fibrate decreases ALP and increases the proportion of patients with normal ALP**

Soret et al. AASLD 2019, Abstr LP6

“Normal bilirubin” in PBC

- 3 995 patients with PBC and normal bilirubin during follow-up



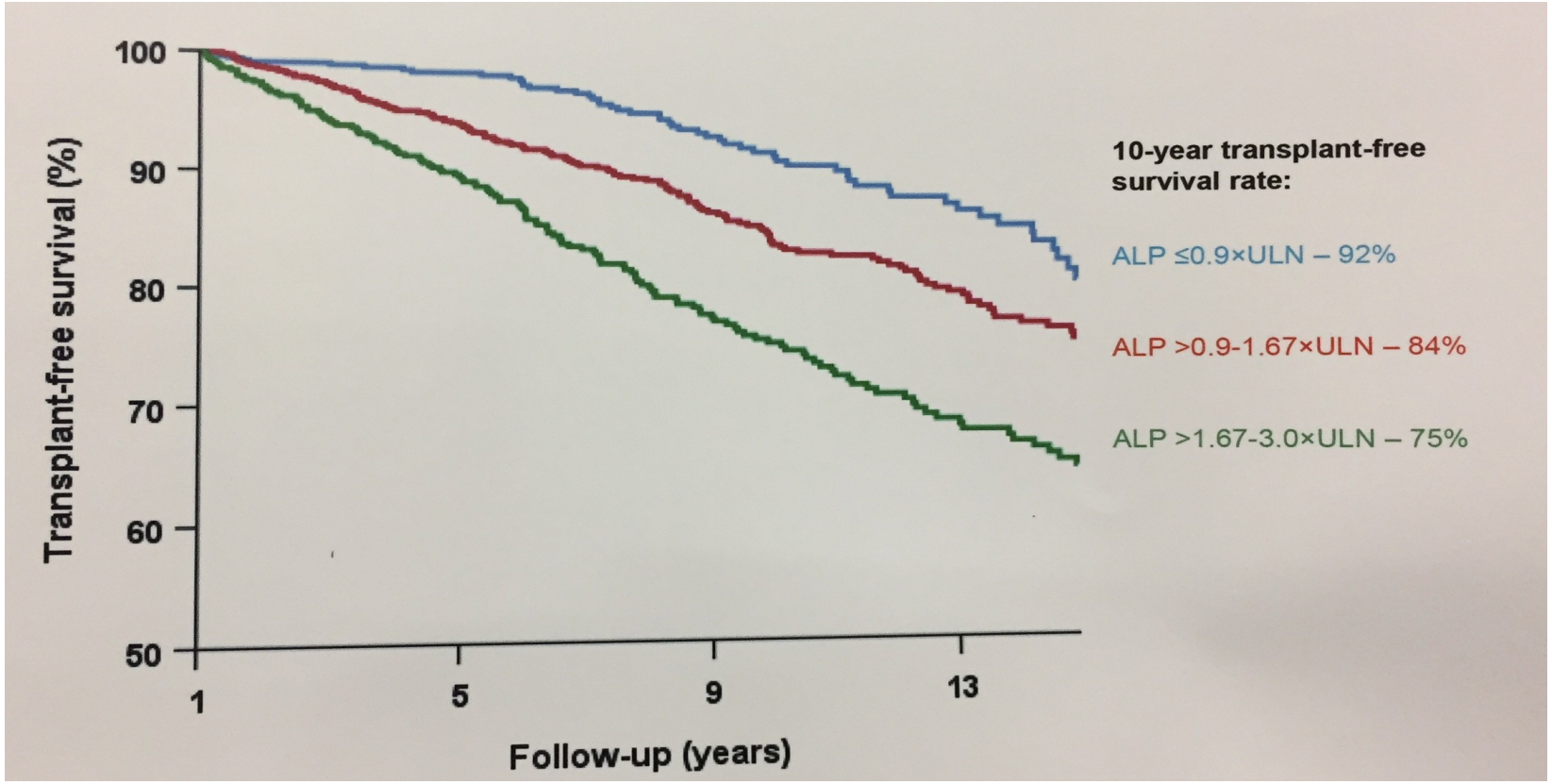


- In patients with PBC and bilirubin level > 0.7xULN, the risk of death/transplantation at long term is higher

Murillo Perez F et al., AASLD 2017 abstr. 70

Which level of ALP should be targeted?

- Global PBC study group : 1806 patients treated with UDCA
- Survival at 10 years according to ALP level after 12 months of treatment



- Aim : normal ALP?

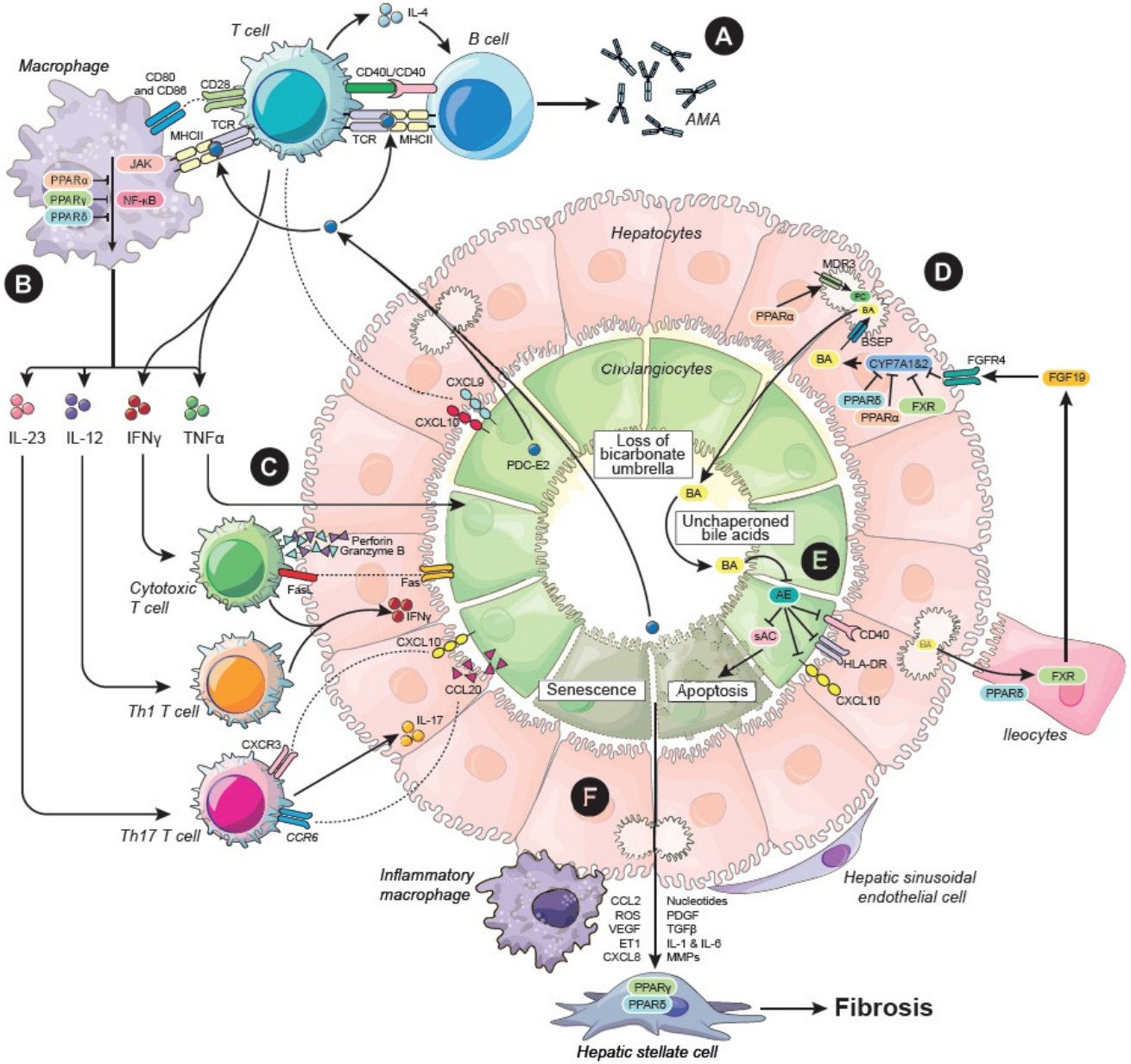
Murillo-Perez et al., AASLD 2018 Abstr. 1909

New treatments for PBC

What are the major goals for new treatments?

- Increase the probability of response (1st & 2nd line)
- Improve tolerance (pruritus)
- Target new pathways
- New endpoints (e.g. normal liver tests)?

Molecular targets



EASL J Hepatol 2017

Molecular targets and cholestatic diseases

TABLE 2. Future and Current Drugs for Cholestatic Liver Disease and Their Proposed Mechanism of Action

(Main) Mechanism	Class	Drug Names	Trial and NCT numbers	Phase
Downstream targets (bile ducts)				
Reduction of bile viscosity; increasing bicarbonate production	UDCA	Urso Falk, Ursochol	Recommended and approved for PBC	
	24-norUDCA	NorUrso Falk[85]	PSC, 01755507	
	Tauro-UDCA	TUDCA[86]	PBC, 01829698, 01857284	2
	TGR5 agonists	INT 777[87]	Not yet in trial	3
Increase phospholipid secretion	PPARα agonists	Fenofibrate[88]	PBC, 02823353,02823366; PSC, 01142323	2
		Bezafibrate[89]	PBC, 01654731; PSC,02701166	3, 3
Anti-inflammatory	CCR2/CCR5 antagonist	Cenicriviroc[90]	PSC, 02653625	2
Reduction of immune activity	Anti-VAP1	BTT1023[91]	PSC, 02239211	2
	Integrin blocker	Vedolizumab	Approved for IBD	
	Anti-CD40	FFP104[92]	PBC, 02193360	
	B-cell depletion	Rituximab	PBC, 02376335	1, 2
	Targets T cells	Abatacept[93]	PBC, 02078882, approved for rheumatoid arthritis	2 2
Upstream targets (hepatocytes, canaliculi, hepatic stellate cells)				
Reduction of bile salt synthesis	FXR agonists	Obeticholic acid[72]	PBC, 01473524 ; PSC, 02177136	3, 2
		PX-104	NAFLD, 01999101	2
		LJN452	PBC, 02516605	2
	FGF19 analogues	NGM 282[94]	PBC, 02135536; PSC, 02704364	2
Reduction of BS load	ASBT inhibitors	LUM 001, SC-435[95]	PBC, 01904058; Alagille, 02061540	2
		A4250[96]	PBC, 02360852	2
	NTCP inhibitor	BAT117213[97]	PBC, 01899703	2
		Myrcludex B[98]	Not yet in trial	
Microbiome	Antibiotics	Vancomycin[99]	PSC, 02605213; 02464020	4
		Xifaxan	PSC, 01695174	1
Anti-inflammatory action	PPARα agonists	See above		
	PPARα/δ agonist	Elafibranor	NASH, 02704403	3
	Phosphodiesterase and TNF inhibitor	Pentoxifylline	PBC, 01249092	2
Reduction of fibrosis	Lysyloxidase inhibitor	Simtuzumab[100]	PSC, 01672853	2

Jansen et al. Hepatology 2017

Molecular targets in PBC

Table 2. Experimental therapies.

1. Management of cholestasis
I. Additional anti-cholestatic drugs:
LJN-452 [ClinicalTrials.gov identifier: NCT02516605]
NGM-282 [ClinicalTrials.gov identifiers: NCT02026401 and NCT02135536]
MBX-8025 [ClinicalTrials.gov identifier: NCT02609048]
GS-9674 (Gilead) [ClinicalTrials.gov identifier: NCT02943447]
Elafibranor [ClinicalTrials.gov identifier: NCT03124108]
II. Immunotherapy agent:
FFP-104 [ClinicalTrials.gov identifier: NCT02193360]
III. Experimental therapies:
Phototherapy
Plasmapheresis
Nasobiliary drainage
Albumin dialysis (Molecular Adsorbent Recirculating System)
2. Management of symptoms
I. Pruritus:
Molecules in trials:
GSK2330672 [ClinicalTrials.gov identifier: NCT01899703]
Lopixibat [ClinicalTrials.gov identifier: NCT01904058]
II. Fatigue:
Rituximab (RITPBC trial) [ClinicalTrials.gov identifier: NCT02376335]

Tropifexor

Seladelpar

Cilofexor, PSC (Trauner et al. Hepatology 2019), PBC?

Linerixibat

Khanna et al. Ther Adv Gastroenterol 2016

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Tropifexor

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Khanna et al. Ther Adv Gastroenterol 2016

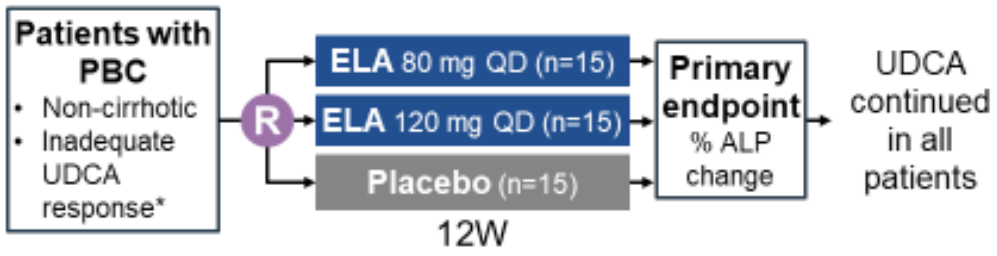
Elafibranor (PPAR-α and δ agonist)

Elafibranor demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to UDCA

BACKGROUND & AIMS

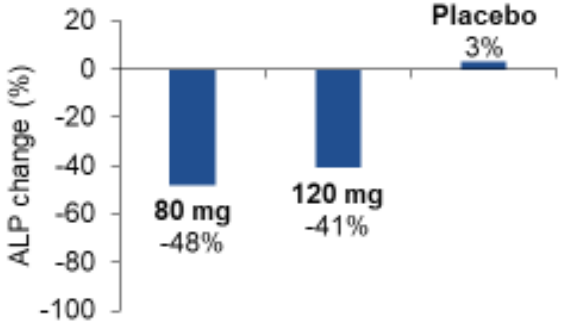
- Up to 40% of UDCA-treated patients have suboptimal response and are at high risk of disease progression
- **Aim:** This phase 2a, double-blind, placebo-controlled study investigated elafibranor (ELA), a dual PPARα/δ agonist, as a new anti-cholestatic treatment for PBC

METHODS



RESULTS

- **Primary endpoint:** ELA demonstrated significant decreases in mean ALP at Week 12



- Highly significant treatment effect vs. placebo (both p<0.001)
  - 80 mg: -52% (95% CI -62.5, -41.5)
  - 120 mg: -44% (95% CI -55.7, -32.1)

*Defined as ALP >1.67x ULN.

Jörn S, et al. ILC 2019; LB-02

Elafibranor (PPAR-α and δ agonist)

Elafibranor demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to UDCA

RESULTS (Cont.)

- Composite endpoint of ALP <1.67x ULN + ALP decrease >15% + total bilirubin <ULN
  - 80 mg: 67% patients (p=0.002); 120 mg: 79% patients (p<0.001) vs. placebo: 6.7%
- GGT also highly significant vs. placebo
  - 80 mg: -39% (p=0.001); 120 mg -40% (p=0.002)
- ELA-treated patients showed improvement in lipid markers,* reduction of inflammatory markers,† and a decrease in C4 (an intermediate of bile acid synthesis)
- By self-reported VAS, patients with BL pruritus (10/group) showed improvement at Week 12
  - 80 mg: -24%; 120 mg: -49%; placebo: -7%
- Both doses of ELA were well tolerated

CONCLUSIONS ELA demonstrated a substantial anticholestatic effect in patients with PBC and inadequate response to UDCA. This was associated with anti-inflammatory and potential antipruritic effects, which make it a promising novel treatment candidate

*Including total cholesterol, low-density lipoprotein, and triglycerides; †IgM, CRP, haptoglobin, and fibrinogen.
Jörn S, et al. ILC 2019; LB-02

EASL The Home of Hepatology

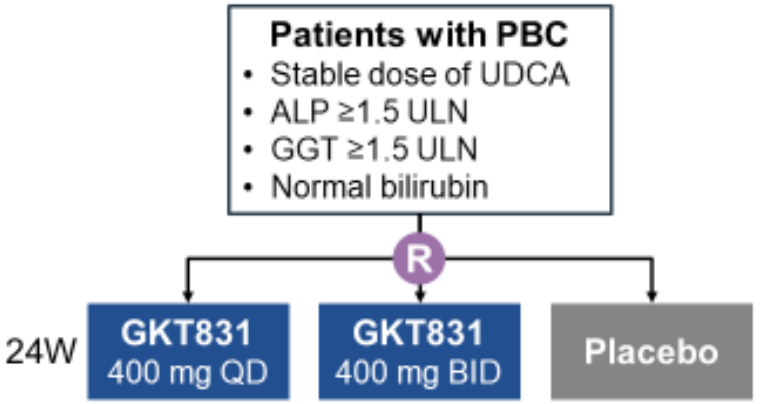
GKT831 (NOX 1/4 inhibitor)

GKT831 in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid: Interim phase 2 efficacy results

BACKGROUND & AIMS

- NOX1/4
  - Produce ROS and modulate intracellular signalling
  - Coordinate activation of multiple inflammatory and antifibrotic pathways in response to cellular stress
- GKT831 is a potent inhibitor of NOX1/4
  - Marked anti-inflammatory and antifibrotic activity in multiple models of advanced cholestatic disease
- This was a 24-week, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of GKT831 in patients with PBC and inadequate response to UDCA
- Study objectives include evaluation of GKT831 effects on biochemical responses, liver injury and fibrosis, and quality of life (pruritus and fatigue)

METHODS



- All subjects continued UDCA throughout
- A predefined interim efficacy analysis was conducted when 92 patients completed 6 weeks of treatment

EASL
The Home of Hepatology

Dalekos G, et al. ILC 2019; GS-02

GKT831 (NOX 1/4 inhibitor)

GKT831 in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid: Interim phase 2 efficacy results

RESULTS

- 111 patients randomized
  - Female: 91%
  - Baseline mean: ALP 312 IU/L; GGT 225 IU/L
- At Week 6, GGT and ALP were significantly reduced vs. placebo (*Table*)
  - Greater GGT reductions achieved in patients with higher baseline GGT (≥2.5x ULN; n=68)
    - -29% for GKT831 400 mg BID vs. -8% for placebo ($p<0.01$)
- Dose-dependent reductions of liver aminotransferases and hsCRP achieved, despite low baseline levels
- Total and conjugated bilirubin unchanged
- Favourable safety profile and no signal for drug-induced pruritus

TABLE Percentage change in markers of liver and bile duct injury vs. baseline at Week 6

	Placebo	GKT831 400 mg QD	GKT831 400 mg BID
GGT	-7	-12	-23*
ALP	-2	-8	-17†

*$p<0.01$ vs. placebo; †$p<0.001$ vs. placebo

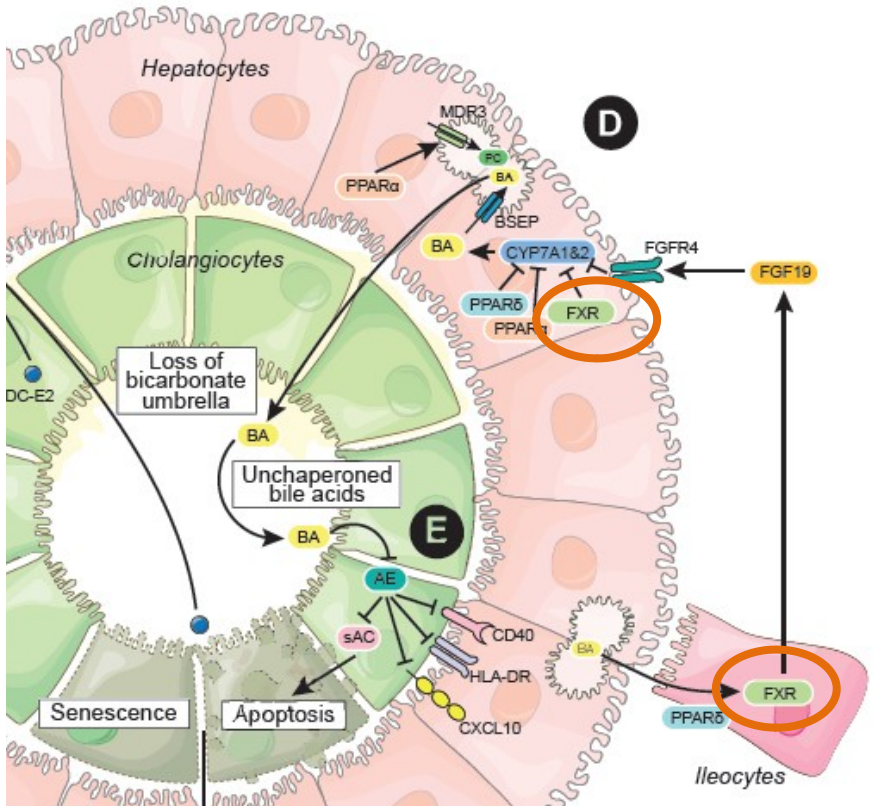
CONCLUSIONS GKT831 achieved rapid dose- and time-dependent reductions in markers of cholestatic bile duct and liver injury. Reductions were highly significant for ALP and GGT in the 400 mg BID group at Week 6. GKT831 is the first non-anticholestatic drug to achieve significant benefits in PBC

Dalekos G, et al. ILC 2019; GS-02

EASL The Home of Hepatology

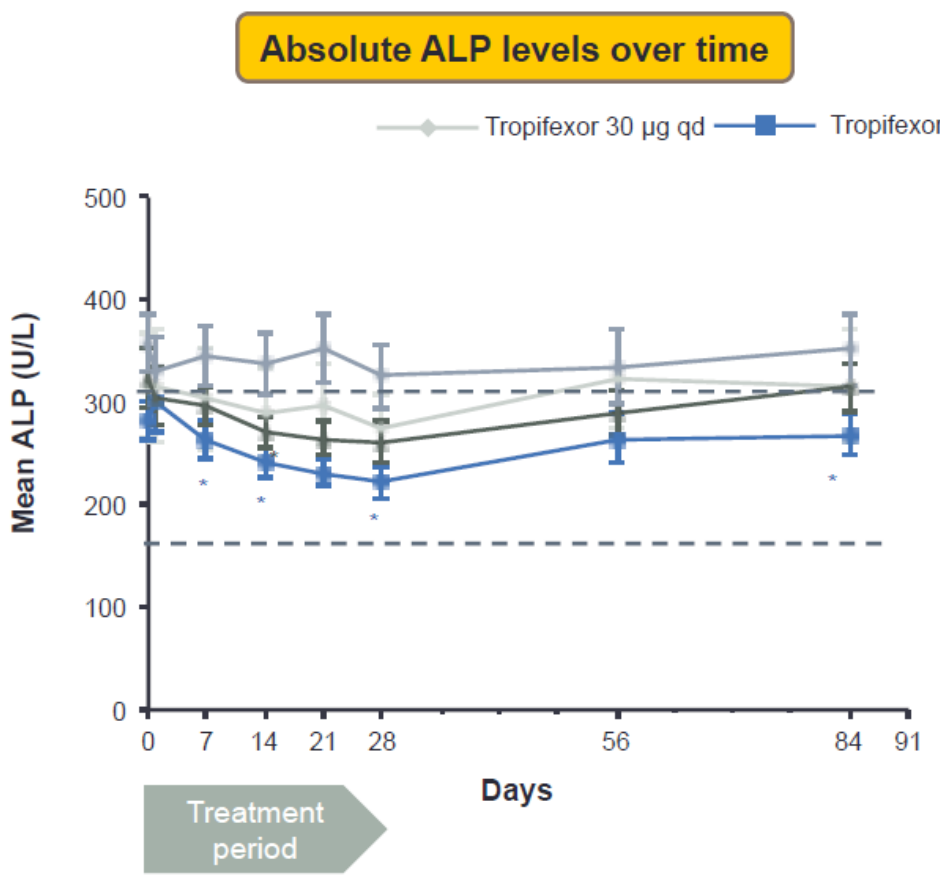
Tropifexor (LJN-452)

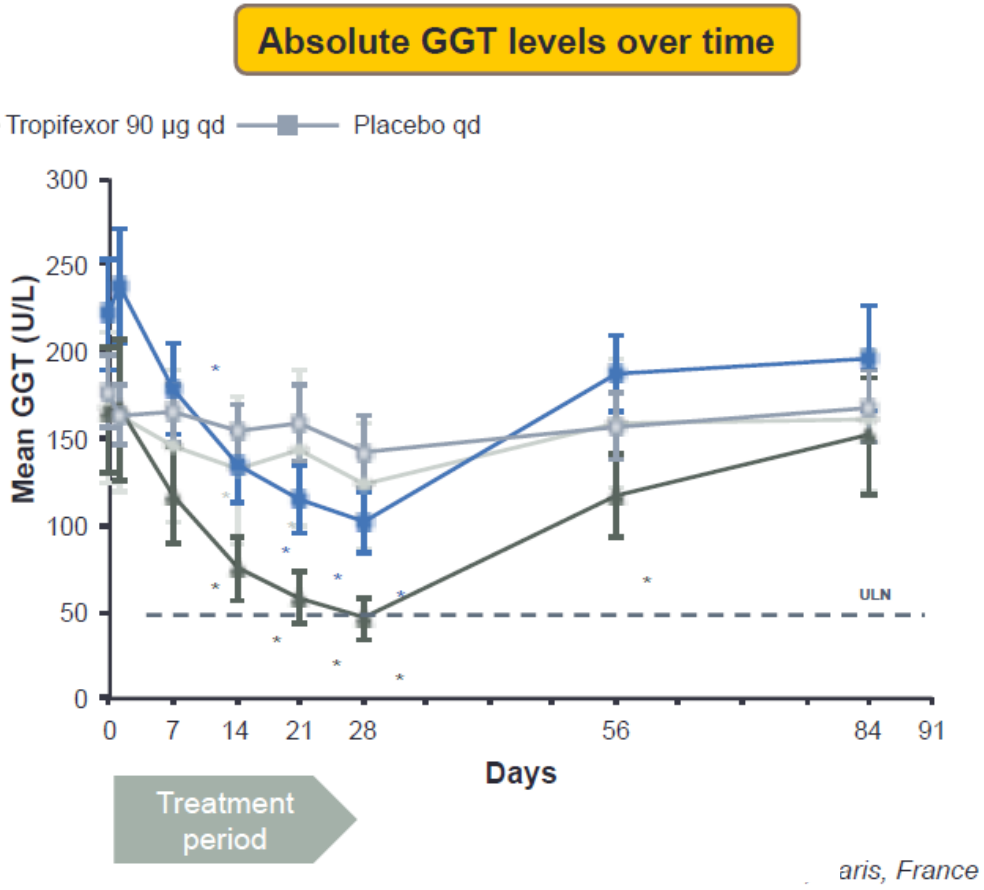
- FXR agonist
- Decreases CYP7A1 expression (cholesterol hydroxylation, first step of bile acid synthesis) and increases FGF-19 synthesis



Tropifexor (LJN-452)

Phase II study (4 weeks)

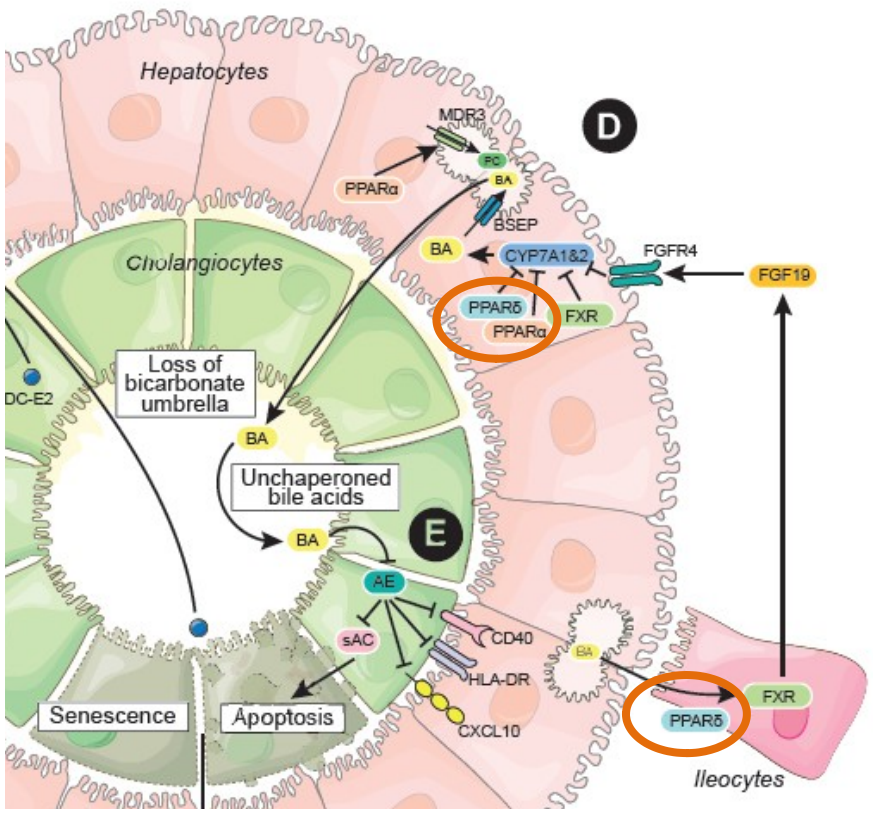


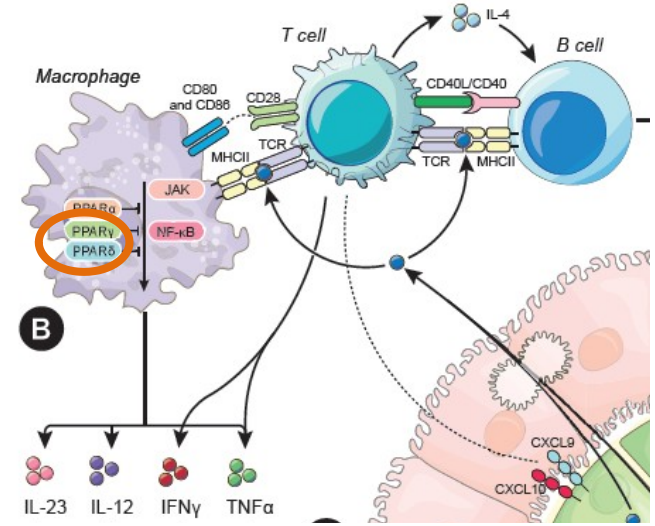


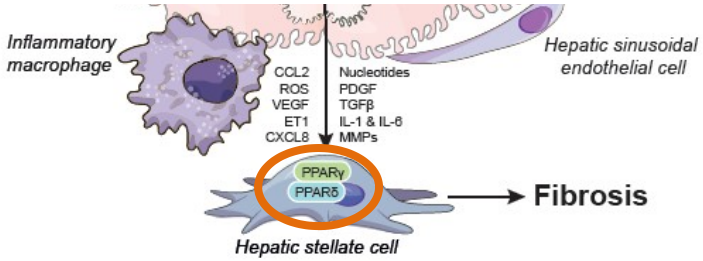
Schramm et al. EASL 2018

Seladelpar (MBX-8025)

- PPAR-δ selective oral agonist
- Decreases CYP7A1 expression
- Potential to reduce inflammation (macrophages) and fibrosis





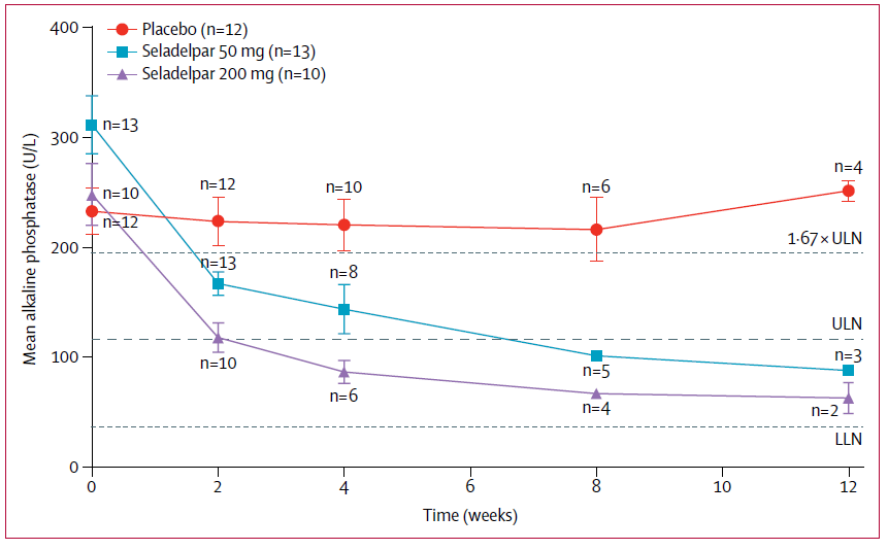


Seladelpar (MBX-8025)

	Week 0	Week 2	Week 4	Week 8	Week 12
Placebo	0/12	1/12	1/10	1/6	0/4
Seladelpar 50 mg	0/13	2/13	4/8	4/5	3/3
Seladelpar 200 mg	0/10	5/10	5/6	4/4	2/2

*Central laboratory upper limit of normal for alkaline phosphatase is 116 U/L.

Table 2: **Number of patients with normalisation of alkaline phosphatase according to week(s) of treatment***



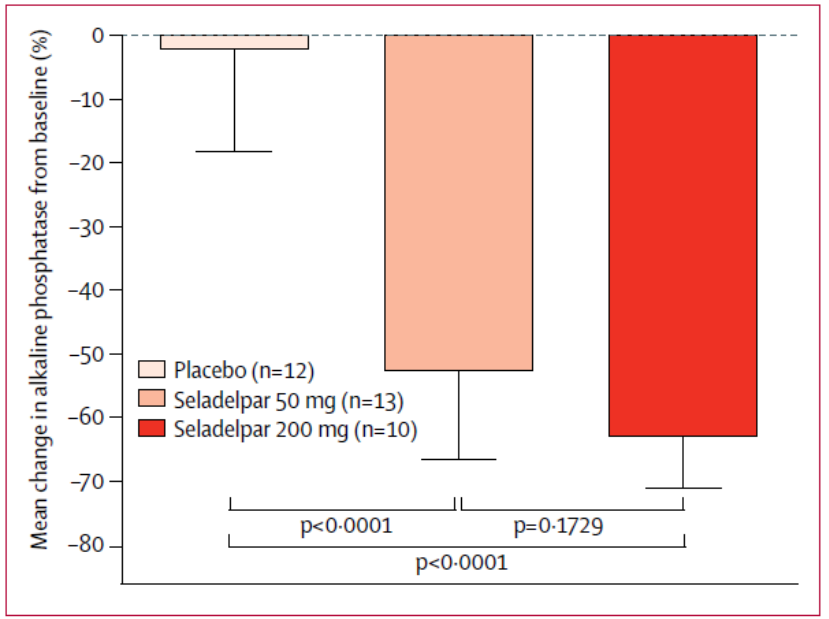


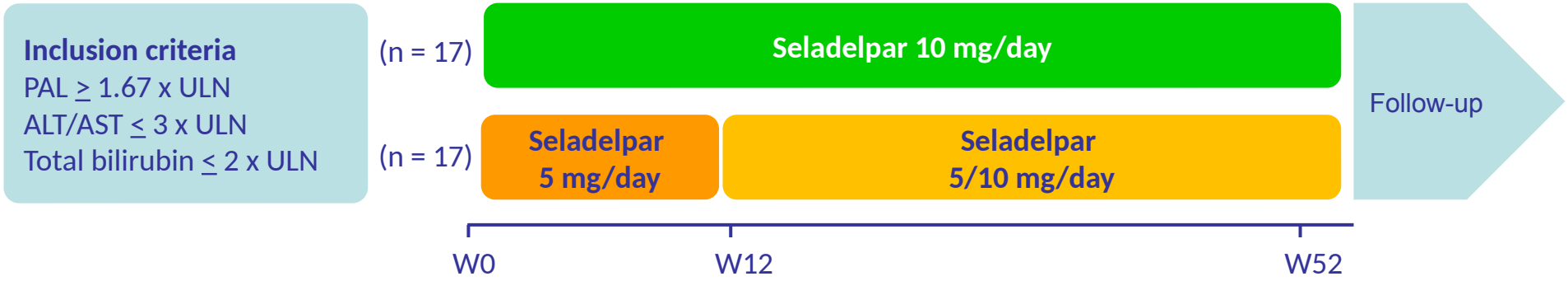
Figure 2: **Mean percentage change in alkaline phosphatase over 12 weeks (last observation carried forward)**

Grade 3 toxicity in 3 patients leading to study discontinuation

Jones et al. Lancet Gastroenterol Hepatol 2017

Seladelpar (MBX-8025)

- Phase II open label trial with adaptative dose in one arm in patients with PBC (stable dose of UDCA or intolerant)



Primary endpoint

- Evolution of ALP from baseline

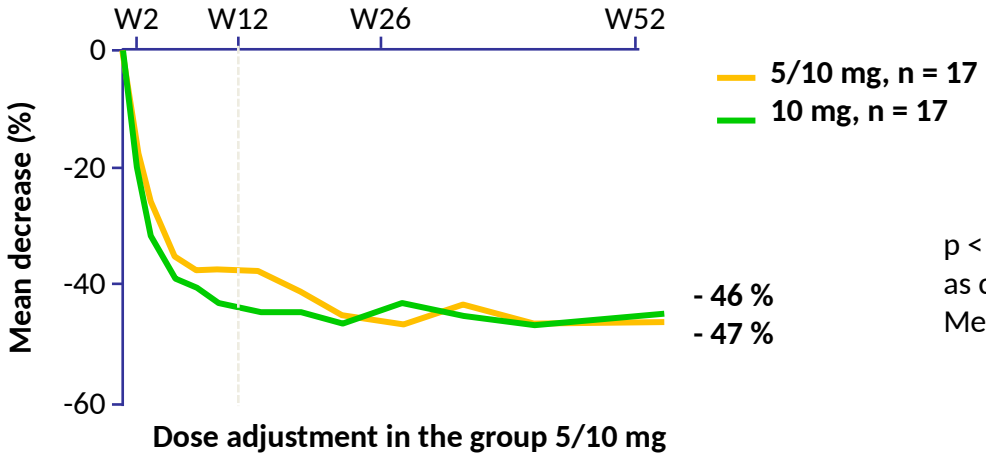
Secondary endpoints

- Biological response defined by :
  - *PAL < 1.67 x ULN and/or decrease >15 % + bilirubin < ULN*
- Normalization of ALP
- Evolution of liver, metabolic and inflammation parameters
- Evolution of pruritus (VAS)

Bowlus et al. AASLD 2018, abstr. LB3

Seladelpar (MBX-8025)

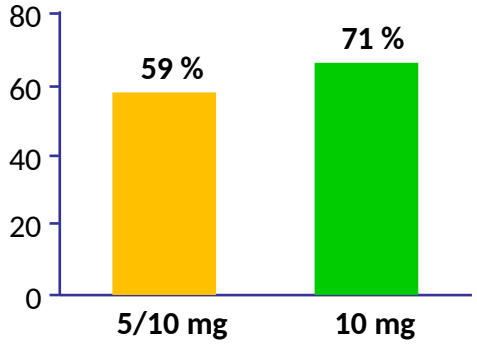
Evolution in ALP level in % from baseline



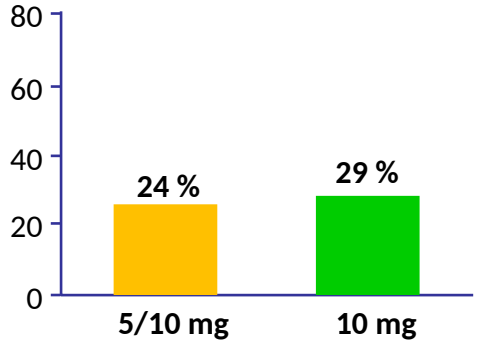
p < 0.0001 in the 2 groups as compared to baseline
Mean ± SEM

Response at Week 52

Composite endpoint (%)



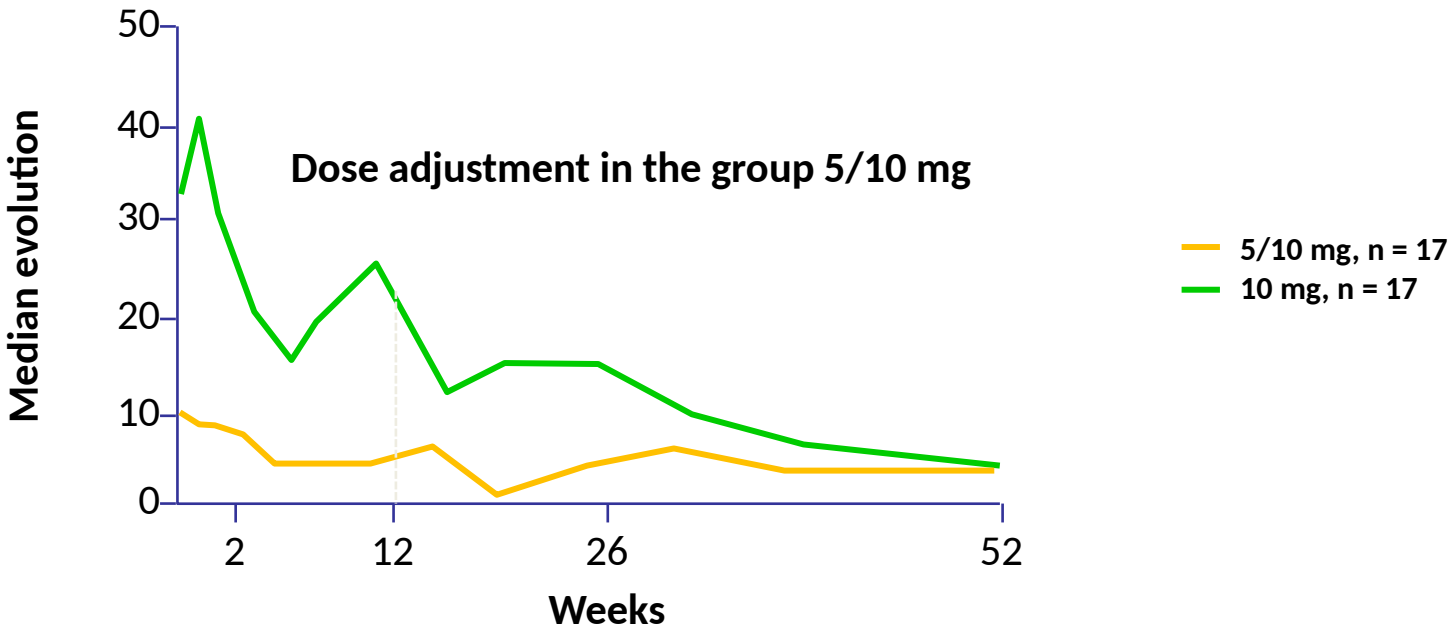
Patients with normal ALP (%)



Bowlus et al. AASLD 2018, abstr. LB3

Seladelpar (MBX-8025)

Pruritus evaluation at Week 52 (VAS)



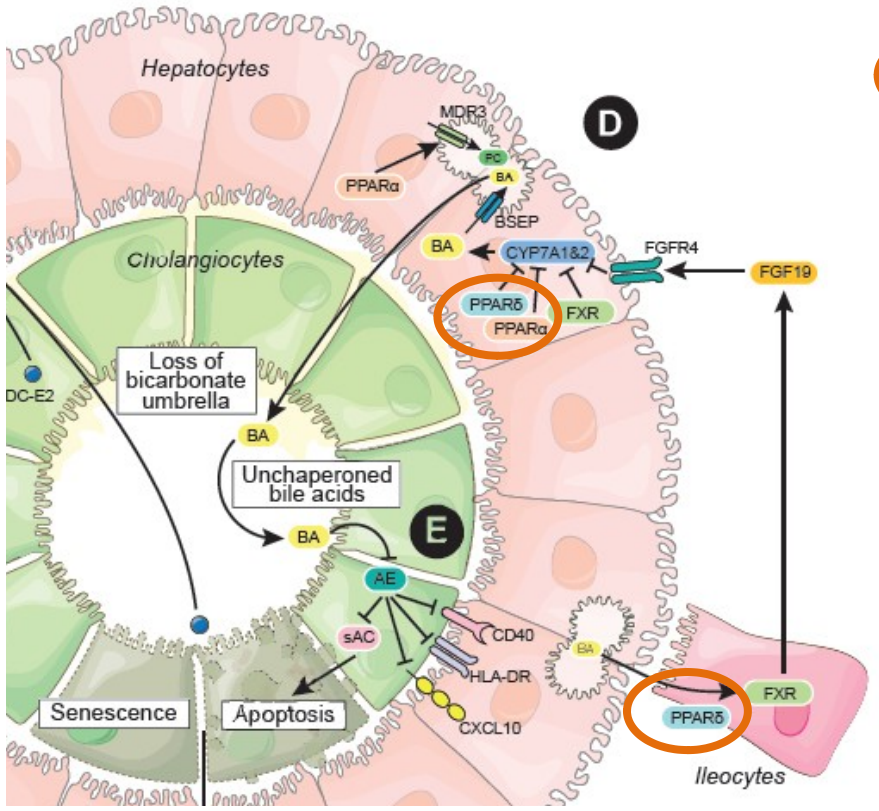
➔ **Safety profile was good, no increased transaminases related to the drug**

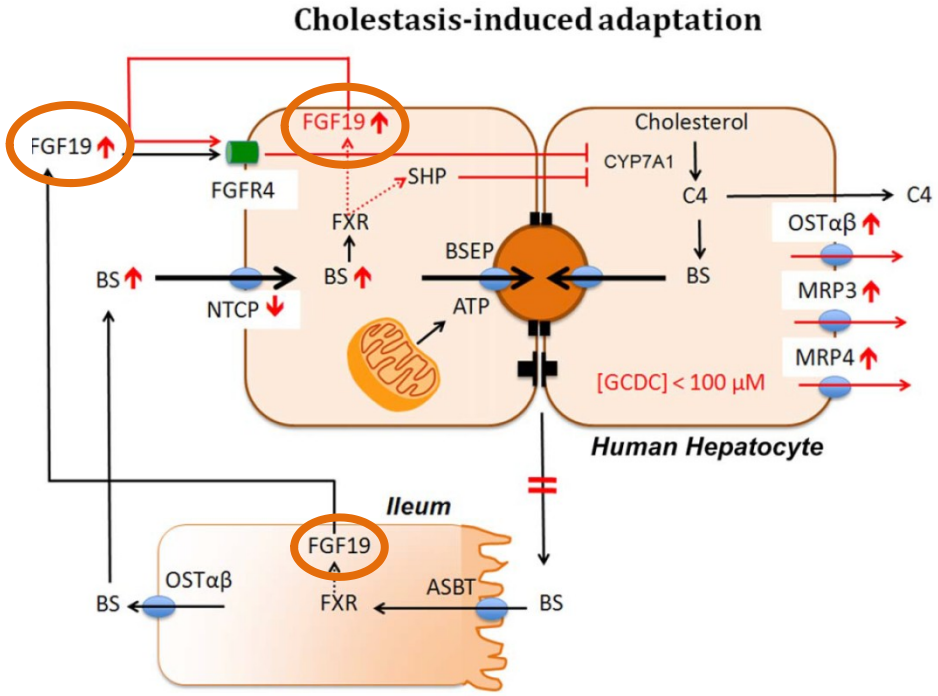
➔ **Results to be confirmed in a phase III trial**

Bowlus et al. AASLD 2018, abstr. LB3

NGM282

- FGF-19 agonist
- FGF-19: hormone produced in the intestine (ileum) after stimulation of FXR
- Decreases CYP7A1 expression (like PPAR-δ and FXR agonists)
- NGM282: no oncogenic activity (unlike FGF-19 in mice)





EASL J Hepatol 2017
Jansen et al. Hepatology 2017

NGM282

In NAFLD:

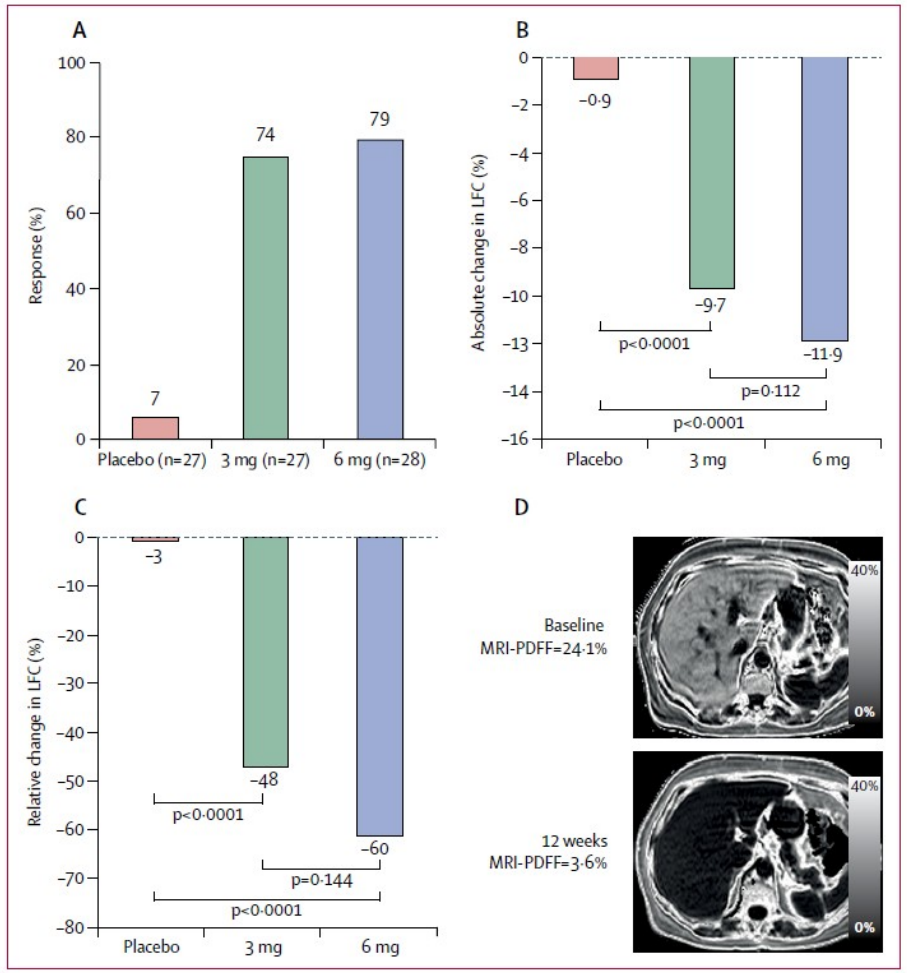
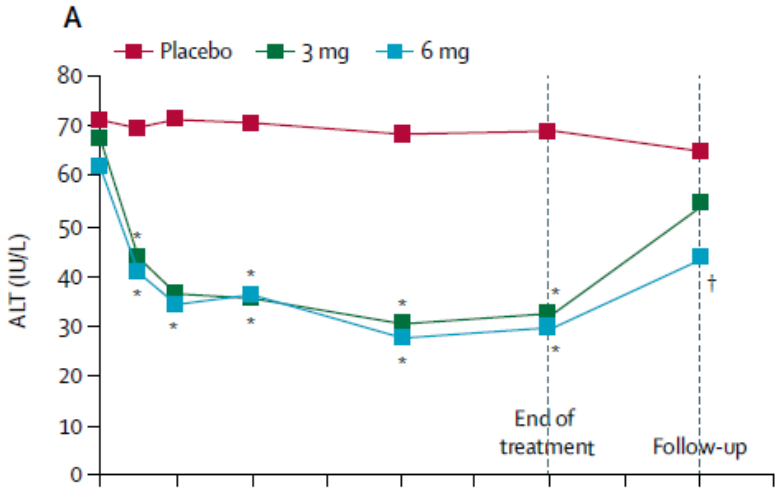


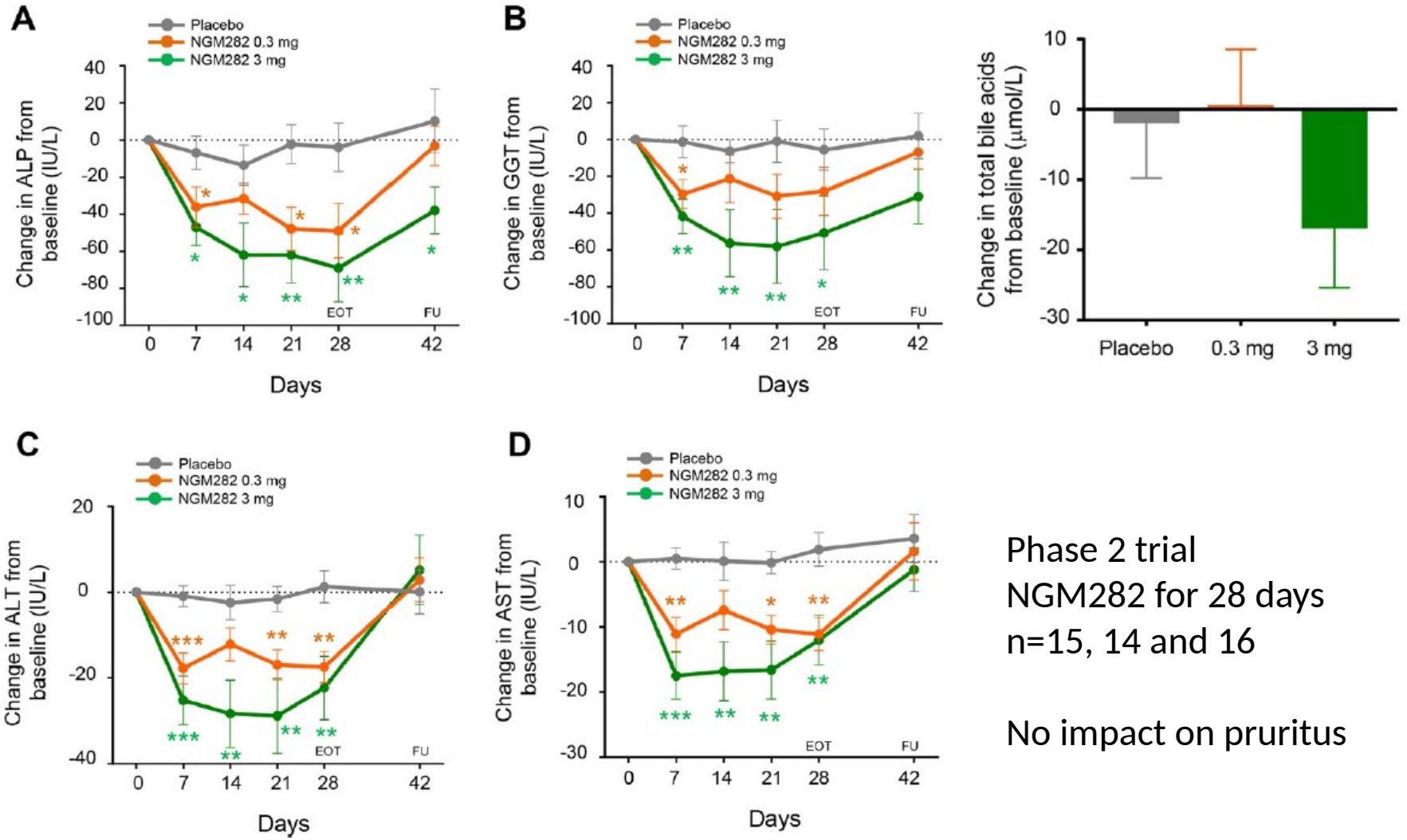
Figure 2: Treatment response (A), absolute change in liver fat content (B), relative change in liver fat content (C), and normalisation of liver fat content with 6 mg NGM282 (D), from baseline to week 12
Absolute and relative change values expressed as least squares means. LFC=liver fat content.
MRI-PDFF=MRI–proton density fat fraction.



- Decreases steatosis
- Increases LDL cholesterol
- Improves NAS and fibrosis scores (Harrison et al. Hepatology 2019)

Harrison et al. Lancet 2018

NGM282 in CBP



Phase 2 trial
NGM282 for 28 days
n=15, 14 and 16

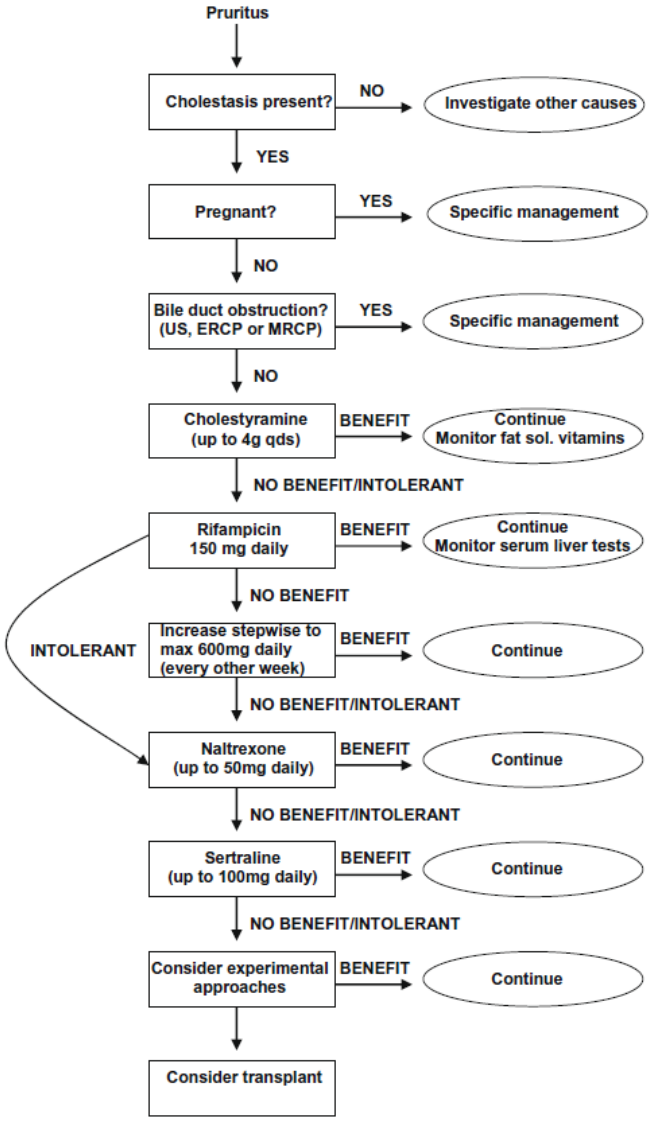
No impact on pruritus

Mayo et al. Hepatol Comm 2018

Summary

- Positive phase 3 trials: OCA, bezafibrate
- Positive phase 2 trials: seladelpar, NGM282, elafibranor, GKT831, tropifexor
- Effects:
  - Decrease in ALP for all
  - Decrease in pruritus: seladelpar, elafibranor, bezafibrate, others?
- Main targets:
  - FXR: OCA, (cilofexor, tropifexor)
  - FGF19: NGM282
  - PPAR: fibrates, seladelpar, elafibranor
  - NOX1/4: GKT831
- Combination therapy?

Mangement of pruritus

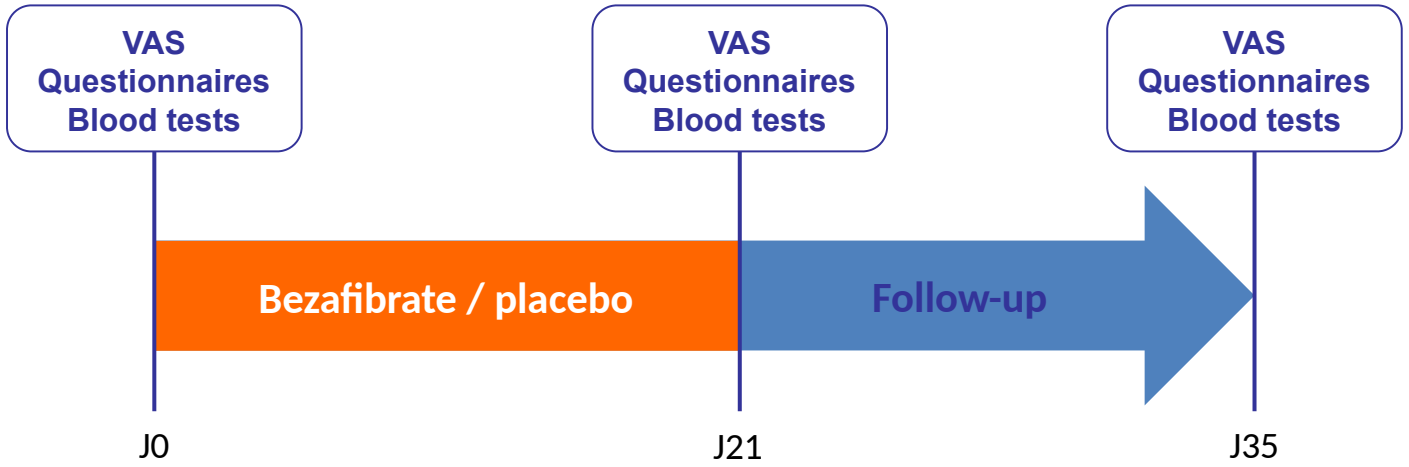


Ileum bile acid transporter (ASBT/IBAT) inhibitors are promising (GSK2330672, Hegade et al. Lancet 2017)

EASL J Hepatol 2009

Bezafibrate and pruritus (FITCH trial)

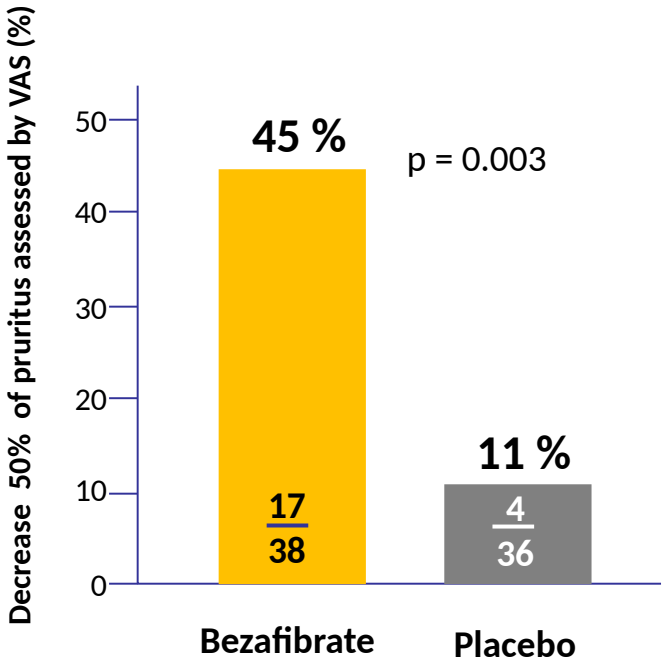
- Double-blinded RCT bezafibrate vs. placebo (400 mg/day) in 74 patients
- **Inclusion criteria:**
  - PBC (n=26), PSC (n=46), secondary sclerosing cholangitis (n=2)
  - Pruritus ≥ 5 (visual analog scale VAS)
- **Primary endpoint:** decrease >50% of pruritus intensity after 21 days of treatment



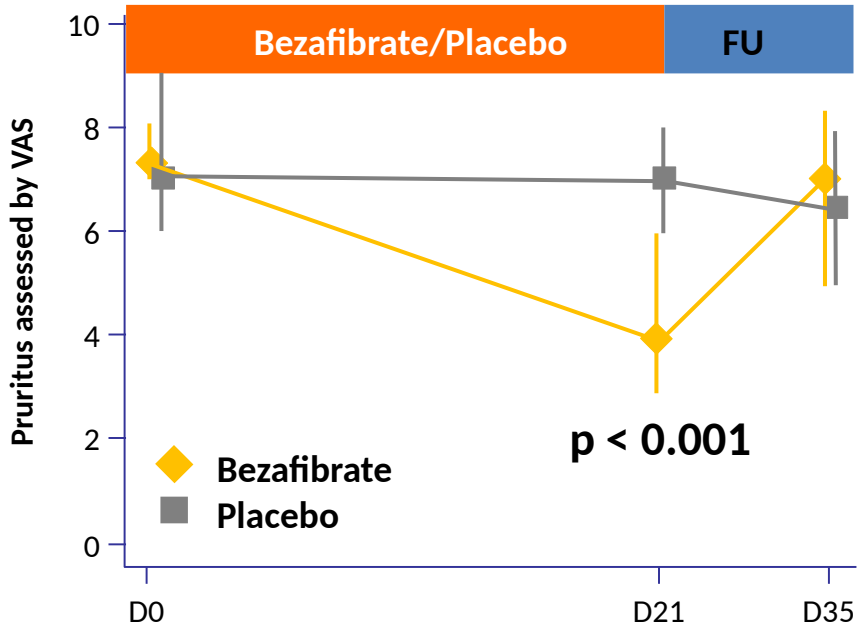
De Vries et al. AASLD 2019, Abstr. 13

Bezafibrate and pruritus (FITCH trial)

Primary endpoint



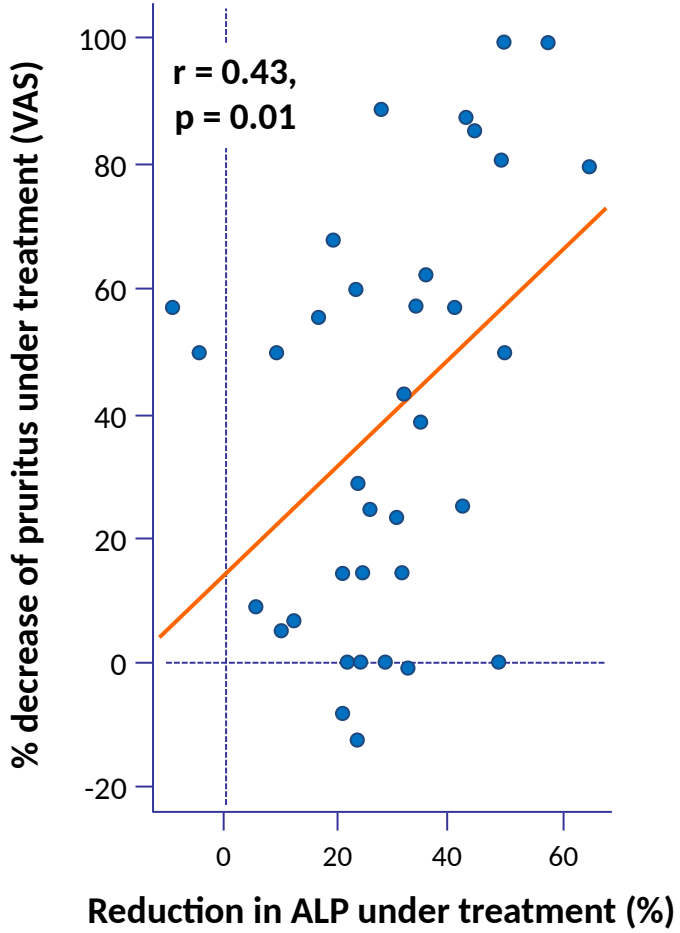
Pruritus evolution



De Vries et al. AASLD 2019, Abstr. 13

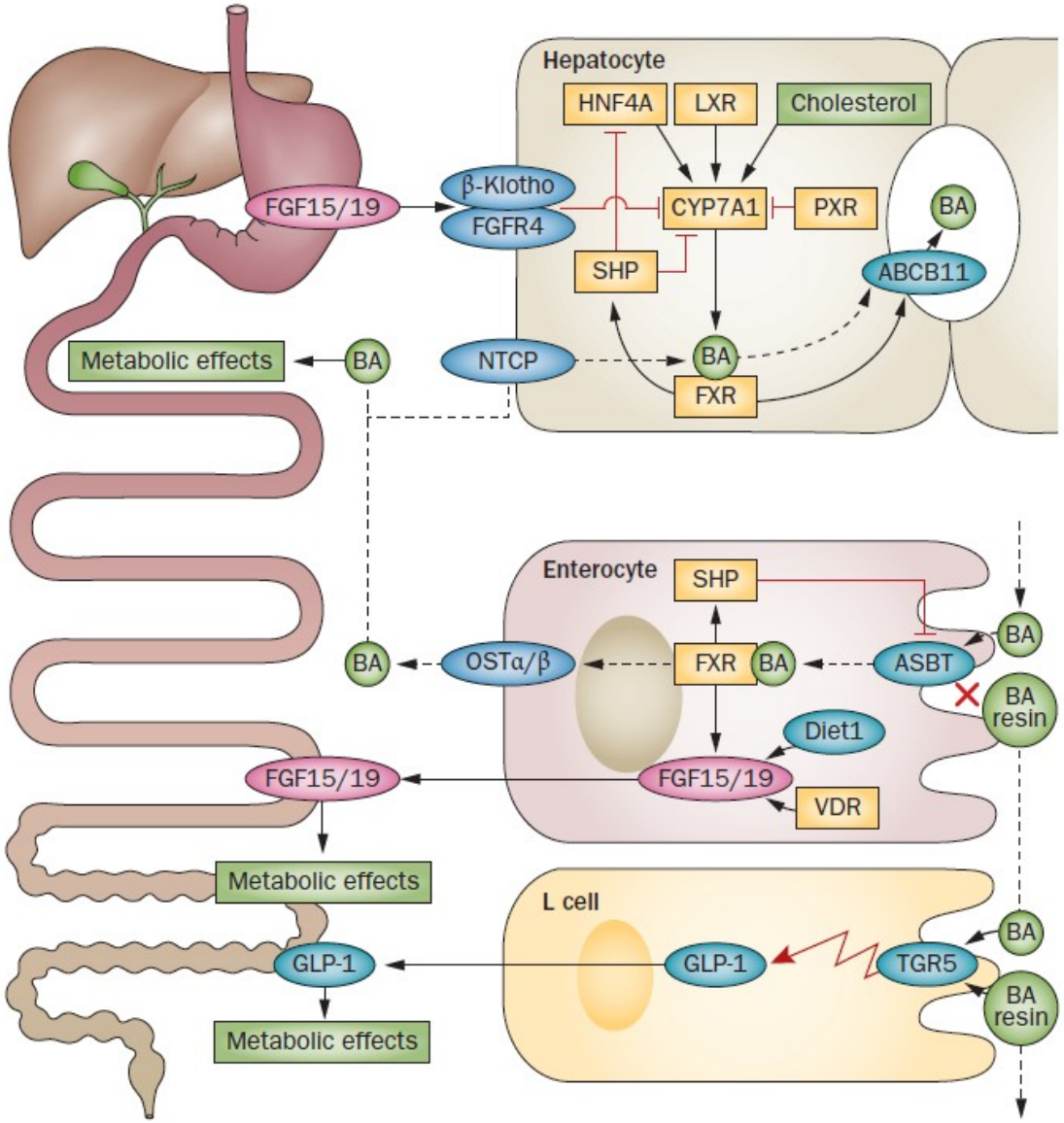
Bezafibrate and pruritus (FITCH trial)

Correlation between pruritus under treatment and ALP



De Vries et al. AASLD 2019, Abstr. 13

Intestine bile acid transport



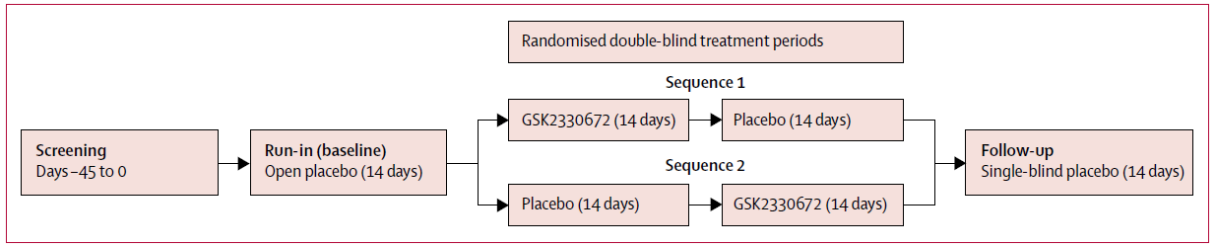
ASBT: Apical Sodium Dependent Bile Acid Transporter

IBAT: Ileal Bile Acid Transporter

Kuipers et al. Nat Rev Endocrinol 2014

Inhibitors of ASBT/IBAT

	Measurement at baseline
Age (years)	52·9 (10·6)
Female (n)	19 (86%)
Body-mass index (kg/m²)	27·2 (4·9)
Bodyweight (kg)	72·8 (13·5)
Duration of primary biliary cholangitis (years)	5 (4·8)
Race	
White (n)	21 (95%)
Asian: Central/South Asian (n)	1 (5%)
Ursodeoxycholic acid (UDCA)	
People taking UDCA during study period (n)	19 (90·4%)
Total daily dose during study period (mg/day)	967 (185·8)
Bodyweight adjusted daily dose during study period (mg/kg/day)	14 (1·7)
Pruritus scores*	
Itch intensity on numerical rating scale (min 0, max 10), trimmed mean	5·33 (2·1)
Primary biliary cholangitis-40 itch domain score (min 3, max 15)	10·5 (3·3)
5-D itch scale (min 5, max 25)	18·7 (3·6)
Laboratory markers*	
Alkaline phosphatase (IU/L)	264 (174·1)
Gamma glutamyl transferase (IU/L)	211 (172·6)
Alanine aminotransferase (IU/L)	59·3 (44·8)
Aspartate aminotransferase (IU/L)	60·8 (35·8)
Total bilirubin (µmol/L)	12·2 (5·5)
Total protein (g/L)	73·32 (5·9)
Albumin (g/L)	41·9 (4·2)
Creatinine (µmol/L)	65·8 (9·1)
Autotaxin activity (nmol/ml per min)	8·2 (4·1)
FGF19 (pg/mL)	162·9 (107·5)
C4 (ng/mL)	13·1 (10·0)
Total bile acids (µM)	48·6 (68·7)



Bicenter randomized phase IIa trial

Linerixibat (GSK-2330672)

22 patients with PBC

Inclusion criterion: refractory pruritus

Treatment given for 14 jours with « cross-over » design

Hegade et al. Lancet 2017

Inhibitors of ASBT/IBAT

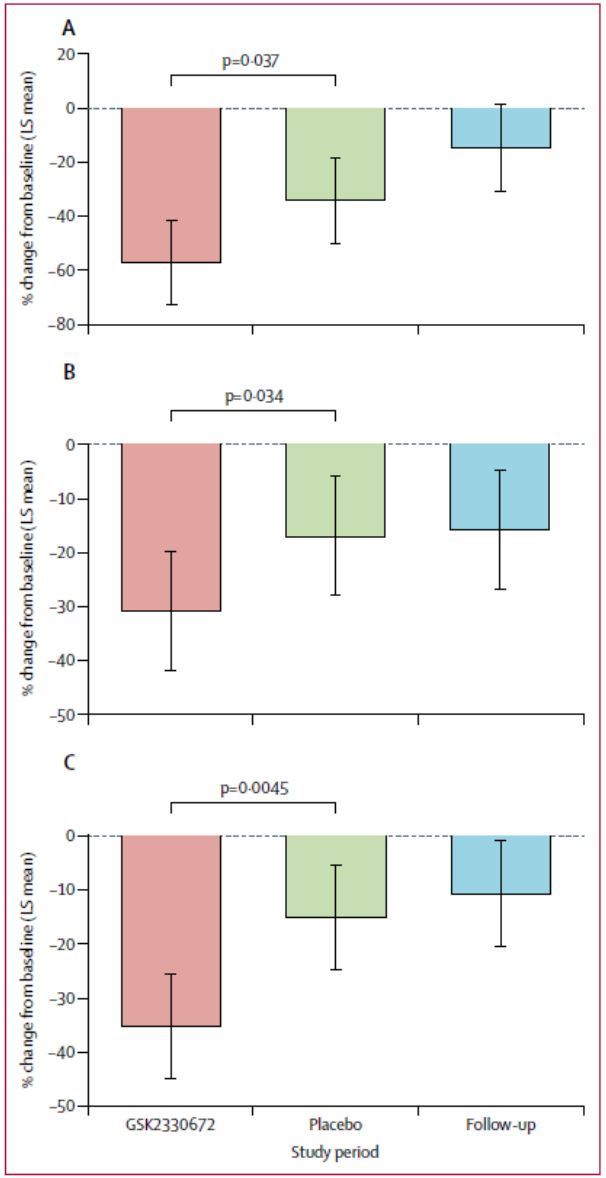


***Figure 3*: Changes from baseline in itch intensity scores according to treatment period**
(A) 0–10 numerical rating scale. (B) Primary biliary cholangitis-40 itch domain score. (C) 5-D itch scale. Error bars are 95% CI. LS=least squares.

	Placebo run-in (n=22), n (%)	GSK2330672 (n=21), n (%)	Placebo (n=21), n (%)
Participants with any adverse event	15 (68)	17 (81)	17 (81)
Gastrointestinal system			
Diarrhoea	1 (5)	7 (33)	1 (5)
Upper abdominal pain	0	3 (14)	1 (5)
Abdominal distension	0	3 (14)	1 (5)
Abdominal pain	0	3 (14)	0
Vomiting	0	1 (5)	2 (10)
Nausea	0	2 (10)	0
Nervous system			
Headache	7 (32)	6 (29)	7 (33)
Dizziness	1 (5)	1 (5)	2 (10)
Paraesthesia	0	0	2 (10)
Infections			
Nasopharyngitis	0	1 (5)	2 (10)
General			
Fatigue	0	0	2 (10)

Adverse events were monitored from day 1 to 56 of the study including follow-up period. Data are in n (%). The listed adverse events (any severity) have an incidence greater than one patient (5%) in any treatment period.

***Table 2*: Summary of adverse events**

Main AE: digestive

Phase III trial ongoing

Hegade et al. Lancet 2017