Painting the new treatment landscape: Novel and emerging therapies for PBC

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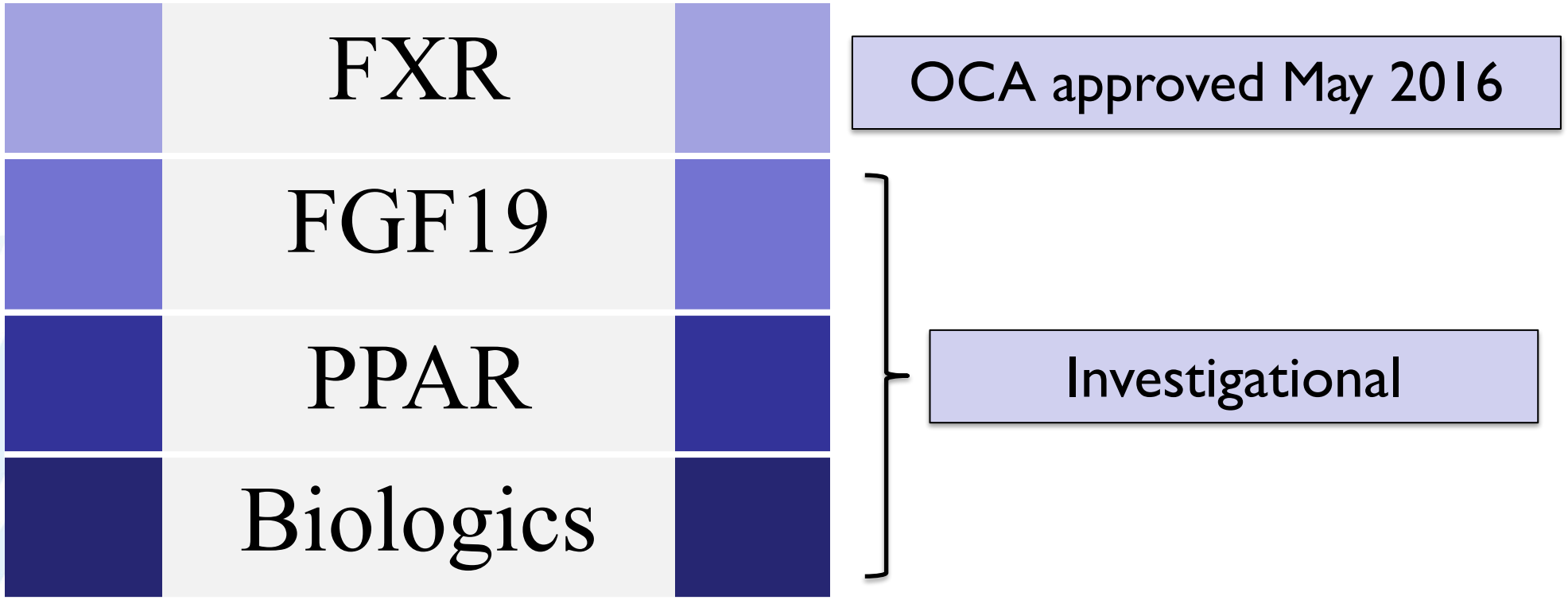
Bile acid-based interventions

	Pharmacological agents under study (examples)	Targets	Natural ligands (examples)
Nuclear receptors	Obeticholic acid, PX-102, GS-9674, LJN452, EDP-305, AKN-083	FXR	Chenodeoxycholic acid, cholic acid
	All-trans retinoic acid	RXR	Retinoic acid (vitamin A)
	Bezafibrate, fenofibrate, ciprofibrate	PPARa	Free fatty acids
	MBX-8025	PPAR delta agonist	
	Budesonide and other corticosteroids	GR, PXR	Cortisol
	Rifampicin, statins, corticosteroids	PXR	Lithocholic acid
	Vitamin D	VDR	1.25-diOH-vitamin D
Membrane receptors	FGF19, NGM 282	FGFR4	FGF19
	Int-777	TGR5	Chenodeoxycholic acid, lithocholic acid
	ASBT inhibitors	ASBT	Conjugated bile acids
Bile acid derivatives	*nor*UDCA	?	

ASBT, apical sodium–bile acid transporter; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; GR, glucocorticoid receptor; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RXR, retinoid X receptor; TGR5, G protein-coupled bile acid receptor 1; UDCA, ursodeoxycholic acid; VDR, vitamin D receptor.

Beuers U, *et al. J Hepatol* 2015;62:S25–37.

PBC therapeutic targets

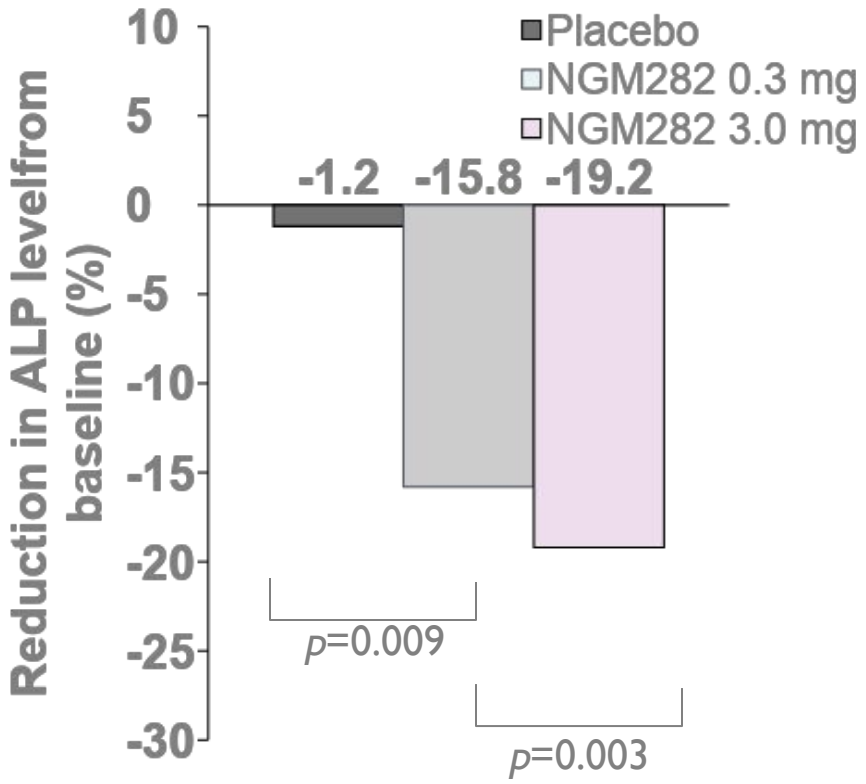


FGF, fibroblast growth factor; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor.

NGM282: Phase II findings of engineered variant FGF19 in PBC

- Double-blind, placebo-controlled trial in patients with PBC and incomplete response to UDCA (n=45)
  - Preliminary findings
    - ALP, ALT, and AST levels decreased significantly
    - Pruritus not exacerbated
    - AEs mild, most common being headache and lower GI symptoms

Comparison of ALP reduction from baseline at on-treatment Day 28

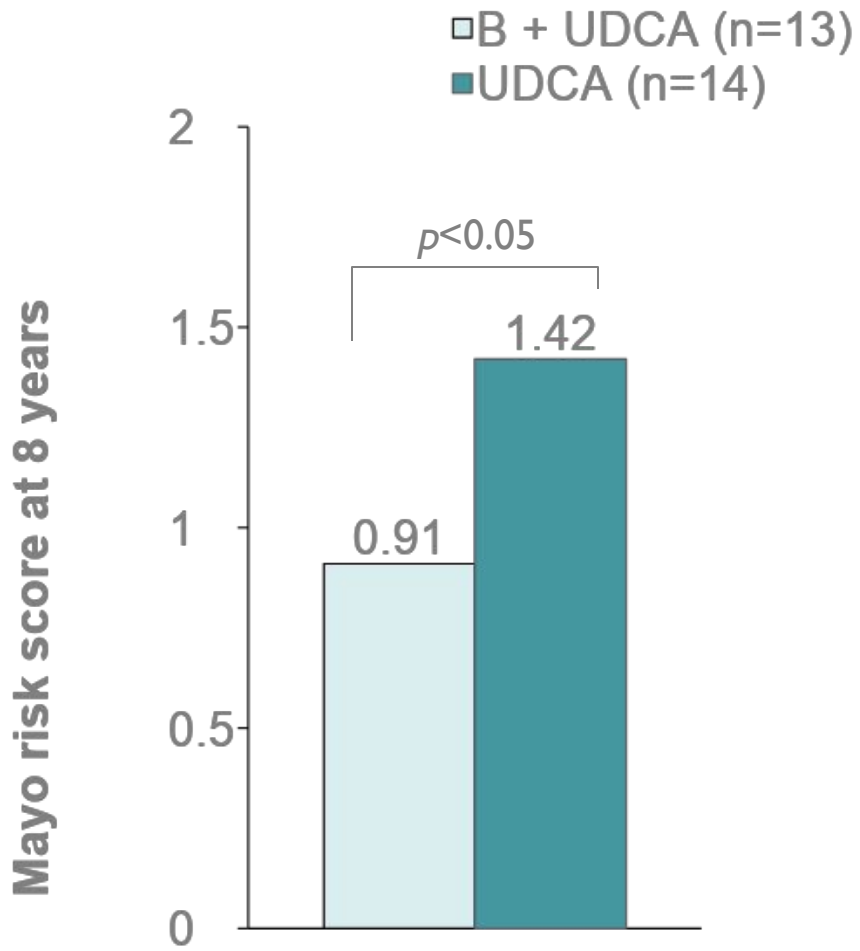


AE, adverse effect; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FGF19, fibroblast growth factor 19; GI, gastrointestinal; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

Mayo MJ, *et al. Hepatology* 2015;62:263A–264A.

Bezafibrate + UDCA: Long-term outcome in UDCA non-responders with dyslipidaemia

- Prospective, randomised, multicenter study (N=27)
  - Therapy continued through 8 years
- Mayo risk score significantly lower with addition of bezafibrate
- Mortality rate and HCC incidence not significantly different between the 2 groups
- **AE: Creatinine levels significantly higher with combination therapy: 0.94 vs 0.56 (*p*<0.05)**
  - "We should pay close attention to adverse events during this long-term combination therapy"



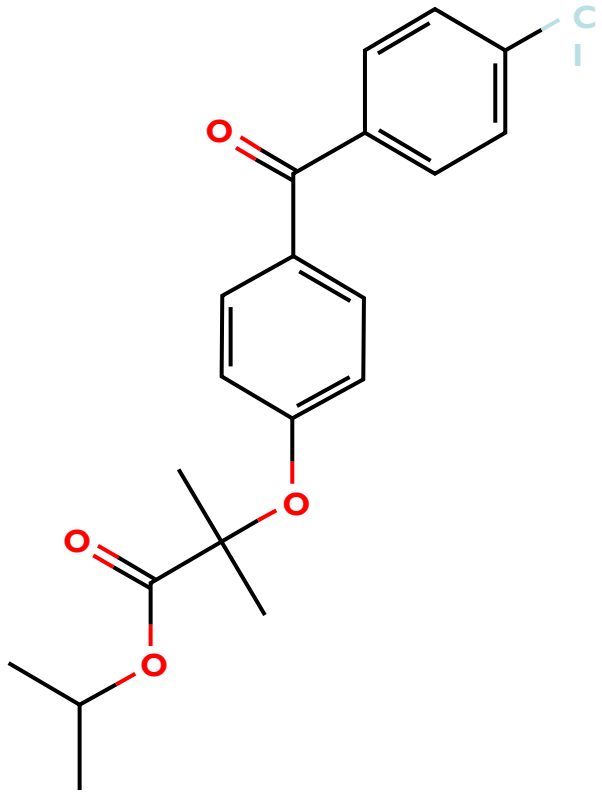
AE, adverse effect; B, bezafibrate; HCC, hepatocellular carcinoma; UDCA, ursodeoxycholic acid.

Hosonuma K, *et al. Am J Gastroenterol* 2015;110:423–31.

Fenofibrate

- Small studies of add-on fenofibrate in patients with no or incomplete response to UDCA have shown favourable results:[1,2]
  - A meta-analysis of fenofibrate (100–200 mg) combined with UDCA reported significant decreases in ALP, γ-GT, total bilirubin and IgM levels[1]
  - The addition of fenofibrate to UDCA was associated with a significant reduction in ALP at 12, 24 and 36 months; however, there was no improvement in UK-PBC risk scores[2]

Structure of fenofibrate



ALP, alkaline phosphatase; Ig, immunoglobulin; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; γ-GT, gamma-glutamyl transferase.

1. Grigorian AY, *et al. Clin Res Hepatol Gastroenterol* 2015;39:296–306; 2. Hegade VS, *et al. Dig Dis Sci* 2016;61:3037–44.

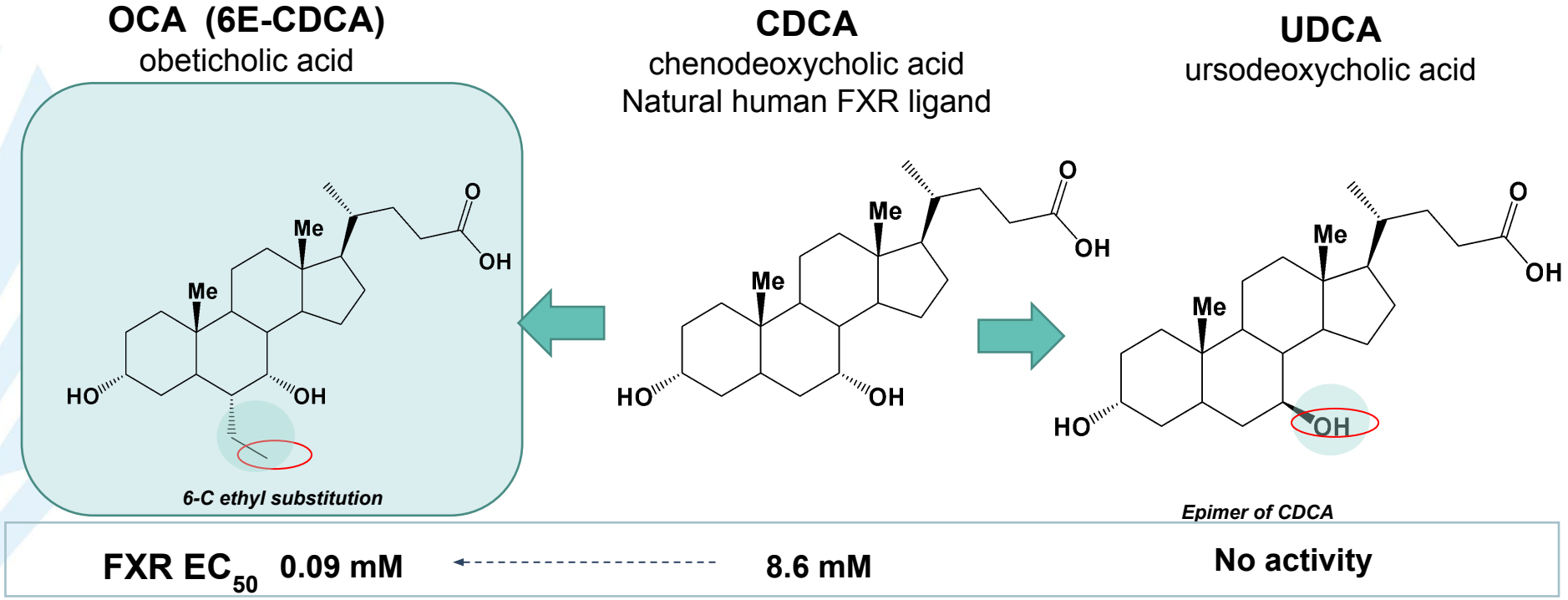
Fibrates in PBC: Summary

- Only small studies available with limited long-term data[1,2]
  - Unknown survival benefit
- Use of fibrates leads to further biochemical improvement in UDCA non-responders[1,2]
- Bezafibrate appears to improve pruritus[3]
- Long-term safety has not been established[4]
  - Concerns with elevated creatinine, heartburn, myalgias
  - Larger studies needed
  - Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including PBC[5]

1. Grigorian AY, *et al. Clin Res Hepatol Gastroenterol* 2015;39:296–306; 2. Hegade VS, *et al. Dig Dis Sci* 2016;61:3037–44; 3. Reig A, Parés A, *et al.* Presented at EASL 2016, Barcelona, Spain: FRI-353; 4. Hosonuma K, *et al. Am J Gastroenterol* 2015;110:423–31; 5. TRICOR (fenofibrate). Prescribing Information 2016.

Obeticholic acid: FXR agonist

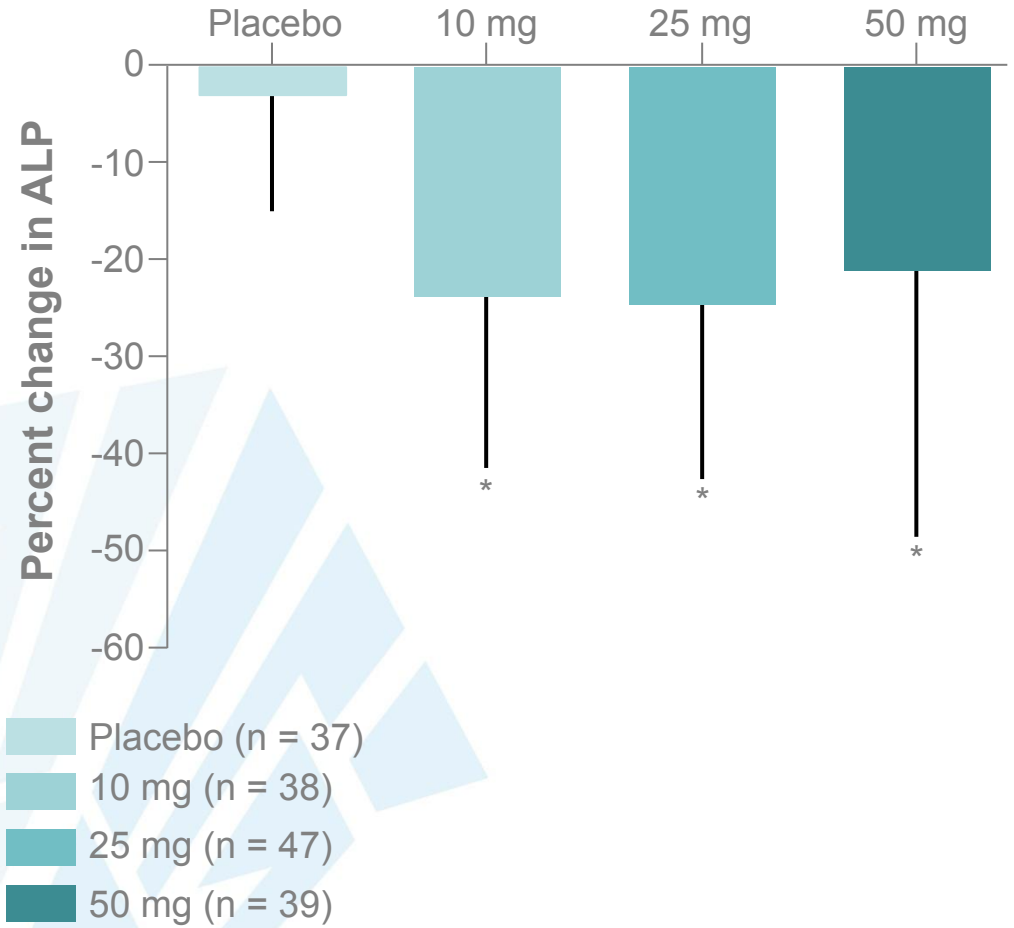
- Modified bile acid and FXR agonist
  - Derived from the primary human bile acid CDCA
  - 100-fold greater potency for FXR relative to CDCA
- FXR properties: Anti-inflammatory, anti-cholestatic, anti-fibrotic and hepato-protective
- UDCA lacks FXR agonist properties



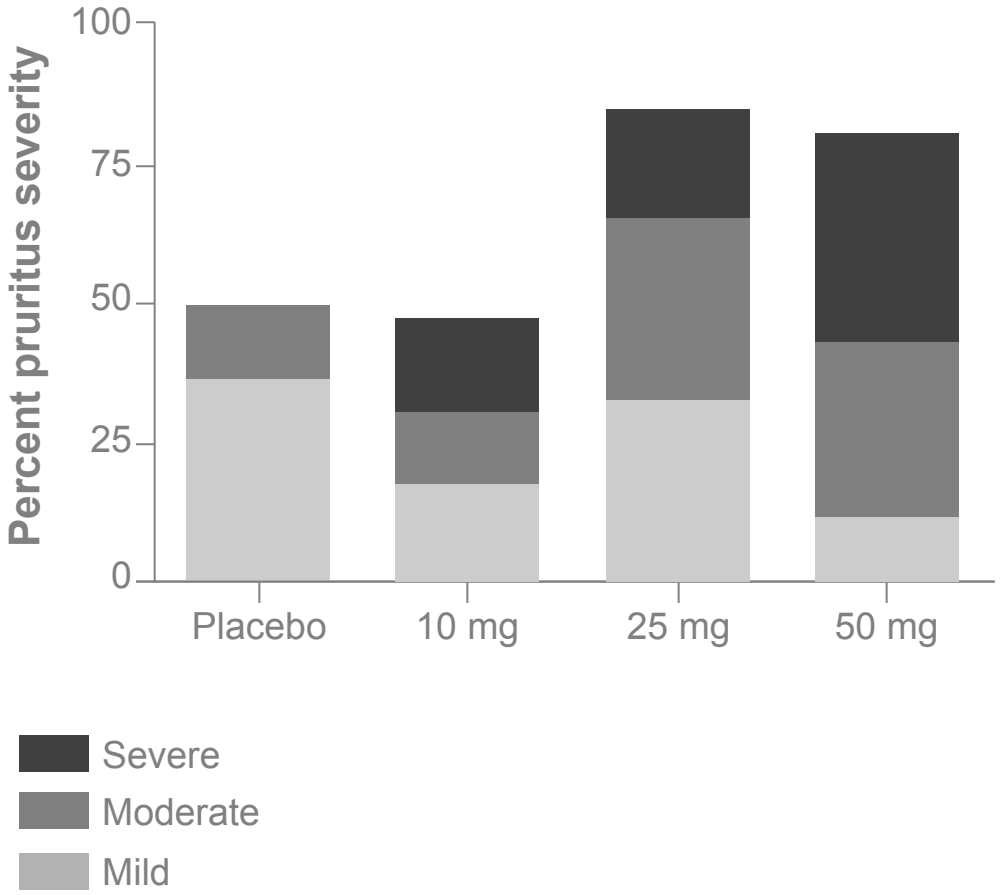
Pellicciari R, *et al. J Med Chem* 2002;45:3569–72.

Obeticholic acid: Phase II study

Percentage reduction in ALP

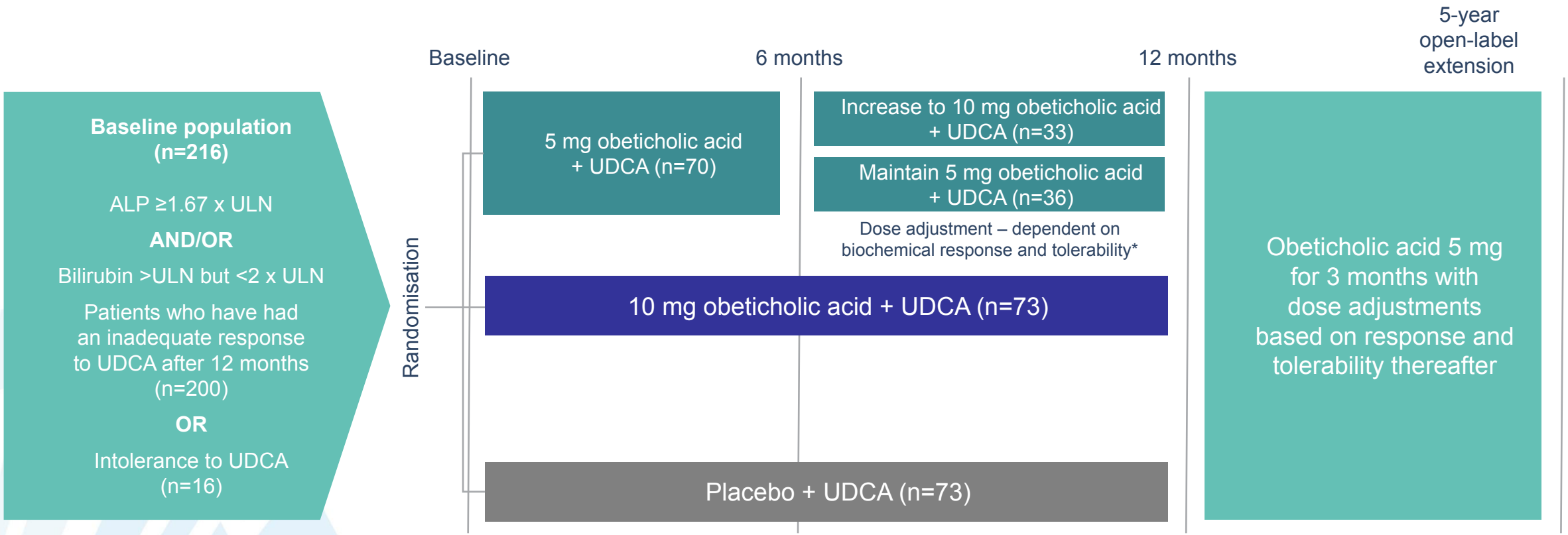


Percentage pruritus severity



*p<0.0001.
ALP, alkaline phosphatase.
Hirschfield GM, *et al. Gastroenterology* 2015;148:751—61.

POISE: Phase III trial design[1,2]



Composite primary endpoint – percentage of patients achieving all three measures:

- ALP <1.67 x ULN
- ALP reduction ≥15%
- Total bilirubin ≤ULN

*Dose was not increased if patients experienced adverse events (such as severe pruritus) or if patients had already met the composite primary endpoint.
ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

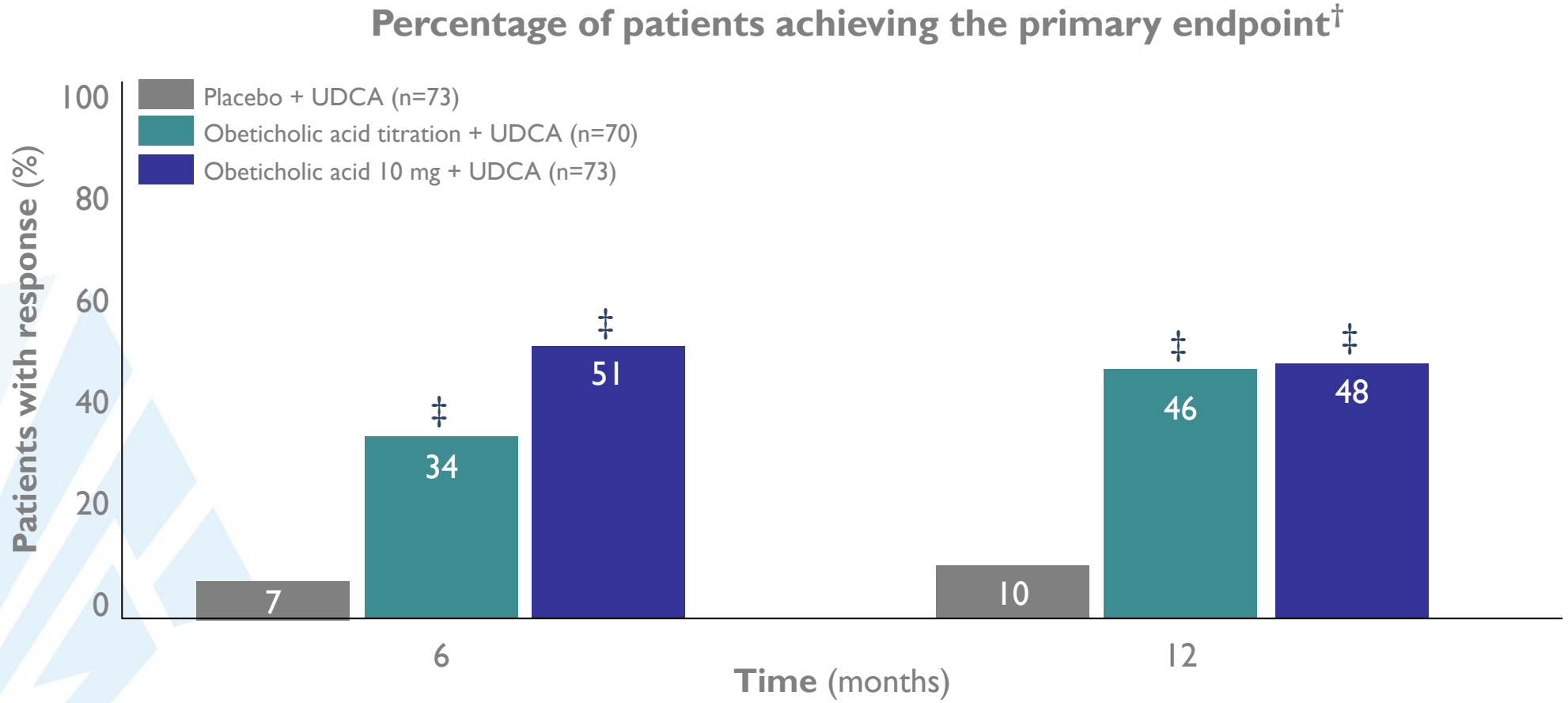
1. Nevens F, *et al. N Engl J Med* 2016;375:631–43; 2. Nevens F, *et al. N Engl J Med* 2016;375:631–43 (supplementary appendix).

Obeticholic acid: Phase III baseline characteristics

	Placebo + UDCA (n=73)	Titration obeticholic acid + UDCA (n=70)	10 mg obeticholic acid + UDCA (n=73)
Age*, years	56 ± 10	56 ± 11	56 ± 10
Female, n (%)	68 (93)	65 (93)	63 (86)
White race, n (%)	66 (90)	67 (96)	70 (96)
ALP*, U/L	327 ± 115	326 ± 116	316 ± 104
Total bilirubin*, mg/dL	0.7 ± 0.4	0.6 ± 0.3	0.7 ± 0.4
Mayo Risk Score*	4.3 ± 1.1	4.3 ± 1.2	4.3 ± 1.2
UDCA use*, n (%)	68 (93)	65 (93)	67 (92)
Daily UDCA dose*, mg/kg	15 ± 4	17 ± 5	16 ± 5
Age at PBC diagnosis*, years	47.3 ± 9.3	47.6 ± 11.7	47.1 ± 10.6
Duration of PBC*, years	8.3 ± 5.5	8.3 ± 5.8	9.2 ± 6.9
Pruritus at baseline*, n (%)	47 (64)	37 (53)	44 (60)

*Values are mean ± standard deviation.
ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.
Nevens F, *et al. New Eng J Med* 2016;375:631–43.

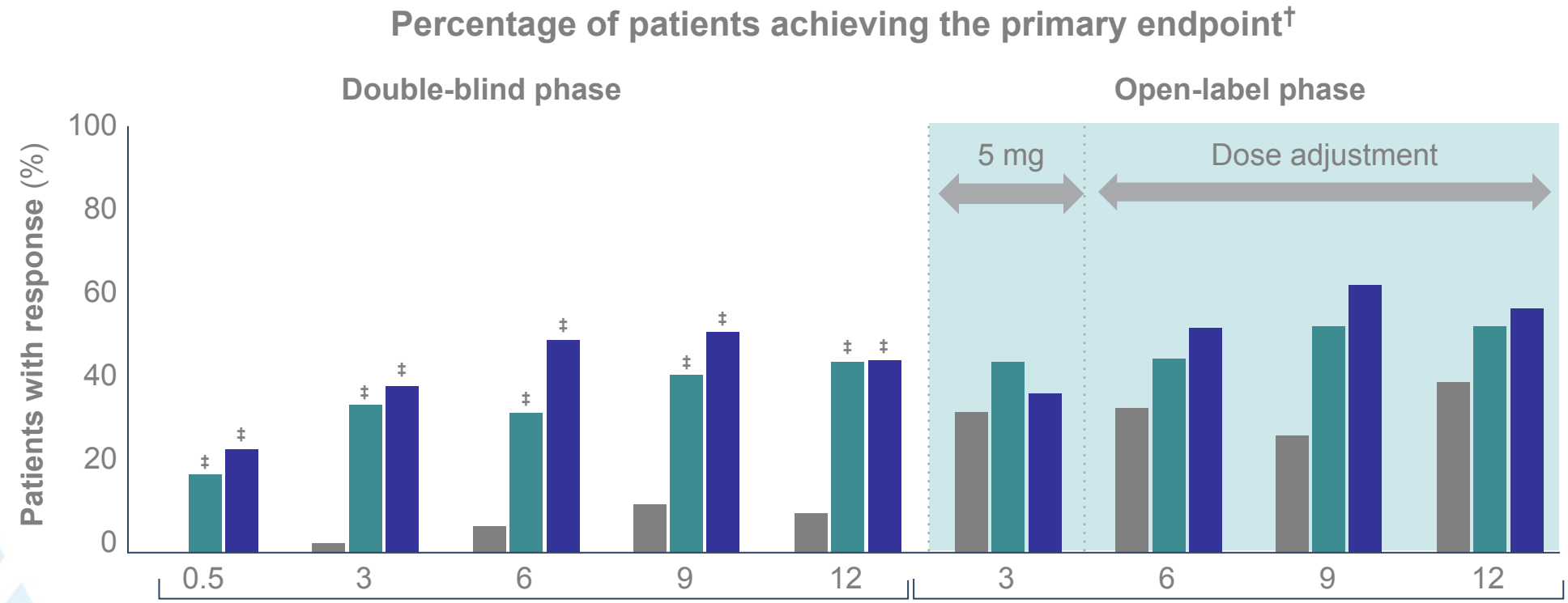
Obeticholic acid + UDCA* was associated with a significantly higher proportion of patients achieving the primary endpoint than UDCA alone[1,2]



*UDCA was withheld from patients intolerant to UDCA; †Percentage of patients achieving all three measures (ALP <1.67 x ULN; total bilirubin ≤ULN; ALP decrease of ≥15%); ‡p<0.0001 vs placebo.
ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. Nevens F, *et al. N Engl J Med* 2016;375:631–43; 2. OCALIVA® (obeticholic acid). Summary of Product Characteristics, 2016.

Obeticholic acid + UDCA* demonstrated sustained improvements in ALP and bilirubin levels with up to 2 years of treatment

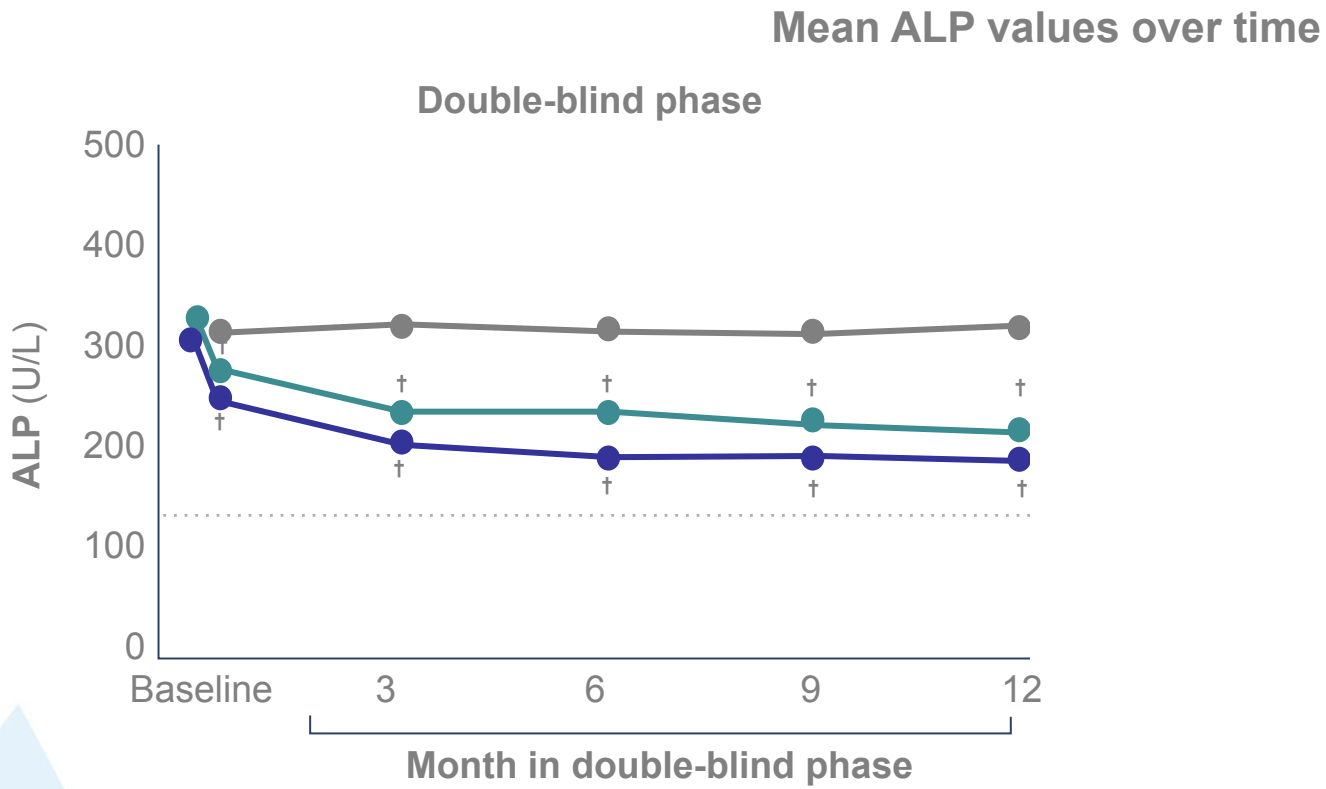


No. of patients									
Placebo + UDCA	73	73	73	73	73	64	60	59	59
Obeticholic acid titration + UDCA	70	70	70	70	70	63	62	62	60
Obeticholic acid 10 mg + UDCA	73	73	73	73	73	64	59	61	59

*UDCA was withheld from patients intolerant to UDCA; †Percentage of patients achieving all three measures (ALP <1.67 x ULN; total bilirubin ≤ULN; ALP decrease of ≥15%); ‡p<0.0001 vs placebo. ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

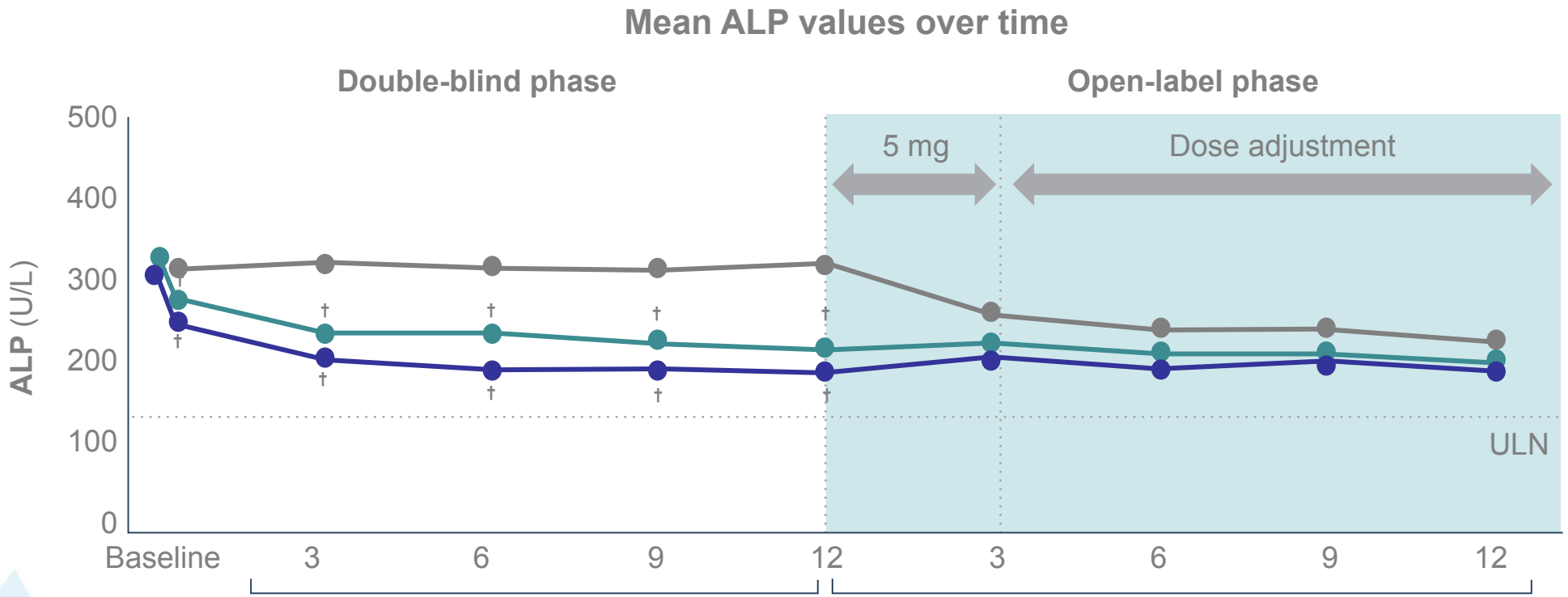
Nevens F, *et al. New Eng J Med* 2016;375:631–43.

Significant reductions in ALP were observed with obeticholic acid + UDCA* as early as 2 weeks and continued up to 12 months versus UDCA alone[1,2]



*UDCA was withheld from patients intolerant to UDCA; †p<0.0001 vs placebo.
ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
1. Nevens F, *et al. N Engl J Med* 2016;375:631–43; 2. Nevens F, *et al. N Engl J Med* 2016;375:631–43 (supplementary appendix).

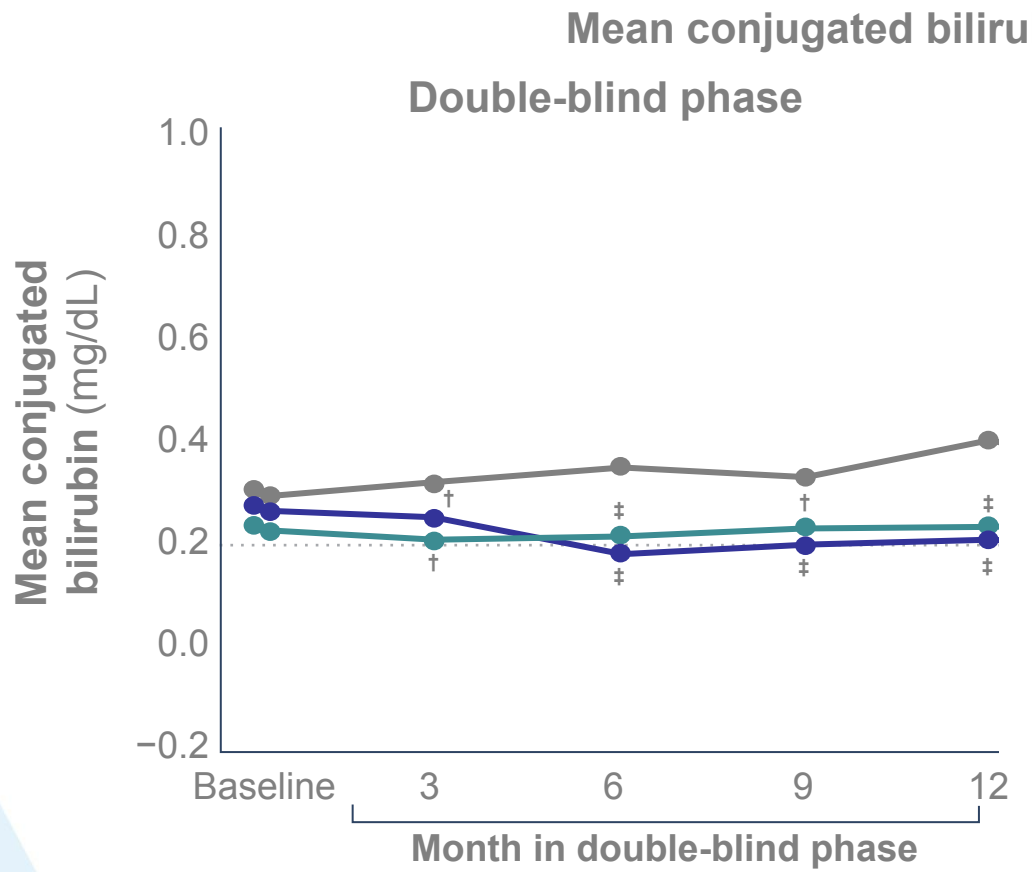
Improvements in ALP observed with obeticholic acid + UDCA* during the double-blind phase were sustained with an additional 12 months of treatment in the open-label phase



No. of patients									
Placebo + UDCA	73	69	71	69	70	64	60	59	59
Obeticholic acid titration + UDCA	70	69	69	66	64	63	62	62	60
Obeticholic acid 10 mg + UDCA	73	66	64	64	62	64	59	61	59

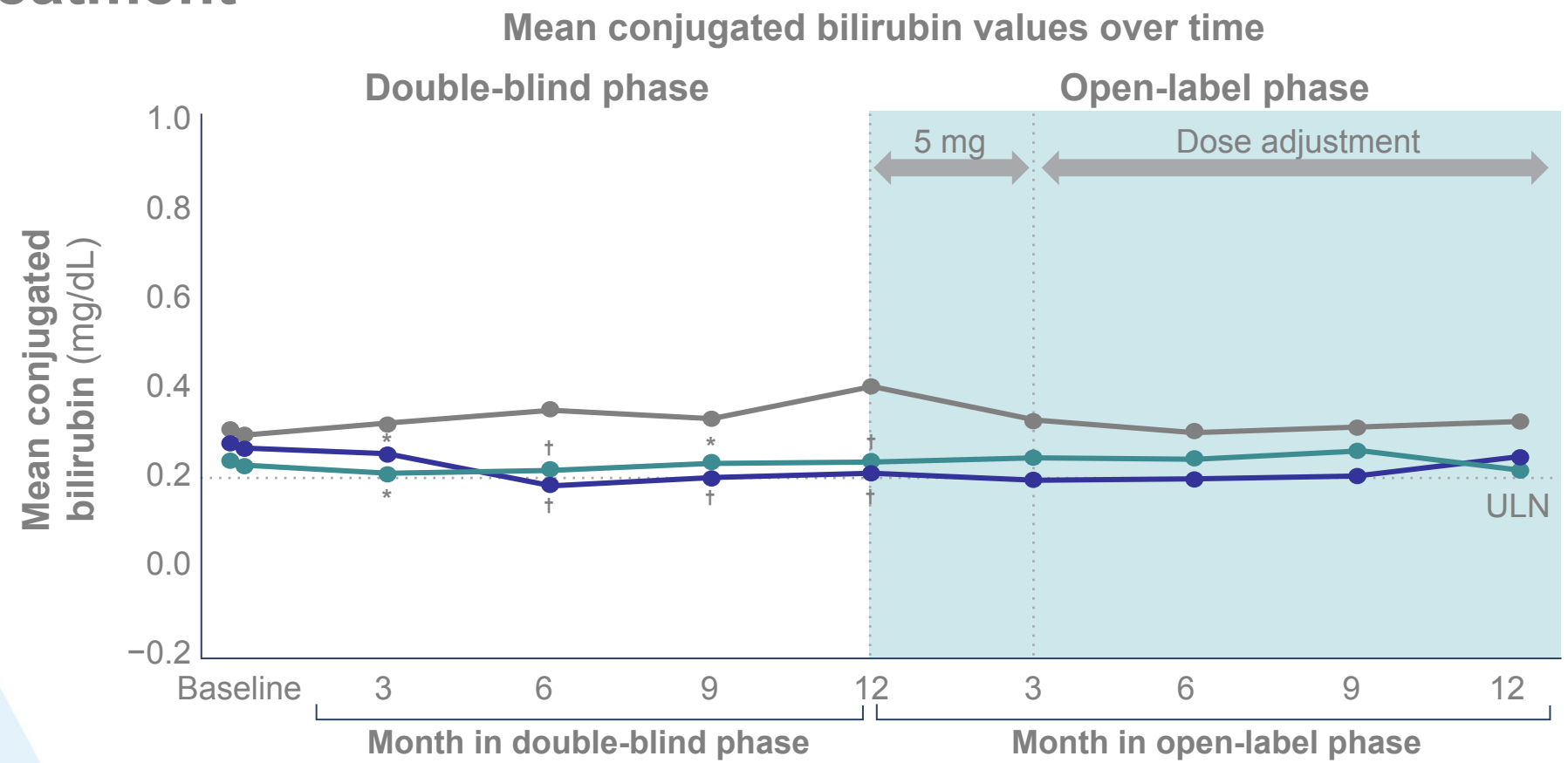
*UDCA was withheld from patients intolerant to UDCA; †$p<0.0001$ vs placebo.
ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Nevens F, *et al. N Engl J Med* 2016;375:631–43.

Obeticholic acid + UDCA* maintained stable conjugated bilirubin levels over 12 months compared with increasing levels in patients receiving only UDCA[1,2]



*UDCA was withheld from patients intolerant to UDCA; †p<0.05 vs placebo; ‡p<0.0001 vs placebo.
UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
1. Nevens F, *et al. N Engl J Med* 2016;375:631–43; 2. Nevens F, *et al. N Engl J Med* 2016;375:631–43 (supplementary appendix).

Stabilisation of conjugated bilirubin was sustained over 2 years of treatment



No. of patients							
Placebo + UDCA	73	71	70				59
Obeticholic acid titration + UDCA	70	69	64				60
Obeticholic acid 10 mg + UDCA	73	64	62				59

*p<0.05 vs placebo; †p<0.0001 vs placebo.
UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Nevens F, *et al. N Engl J Med* 2016;375:631–43 (supplementary appendix).

Obeticholic acid is generally well tolerated[1,2]

- The most common adverse reactions reported during treatment with obeticholic acid were pruritus and fatigue[1,2]

POISE trial adverse events[2]

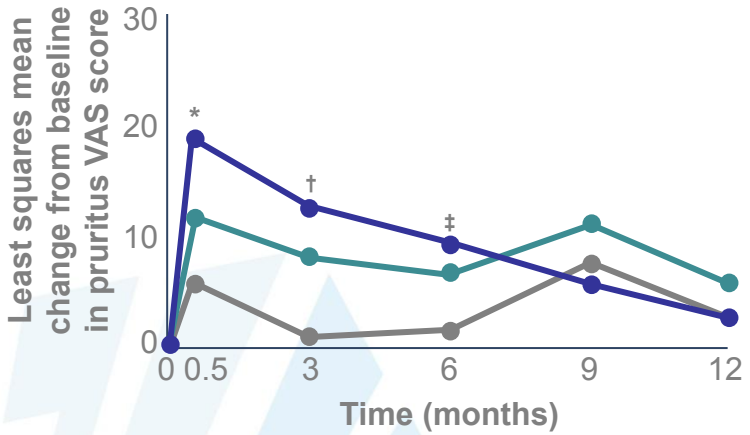
AE in ≥10% of patients in any arm	Placebo + UDCA n (%), n=73	Titration + UDCA n (%), n=70	10 mg + UDCA n (%), n=73	OLE n (%), n=193
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)
Nasopharyngitis	13 (18)	17 (24)	13 (18)	45 (23)
Headache	13 (18)	12 (17)	6 (8)	36 (19)
Fatigue	10 (14)	11 (16)	17 (23)	50 (26)
Nausea	9 (12)	4 (6)	8 (11)	28 (15)
Diarrhoea	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)

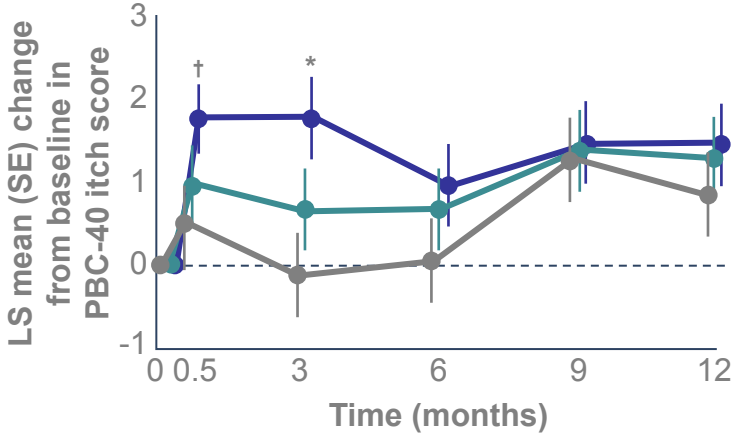
AE, adverse event; OLE, open-label extension; UDCA, ursodeoxycholic acid.

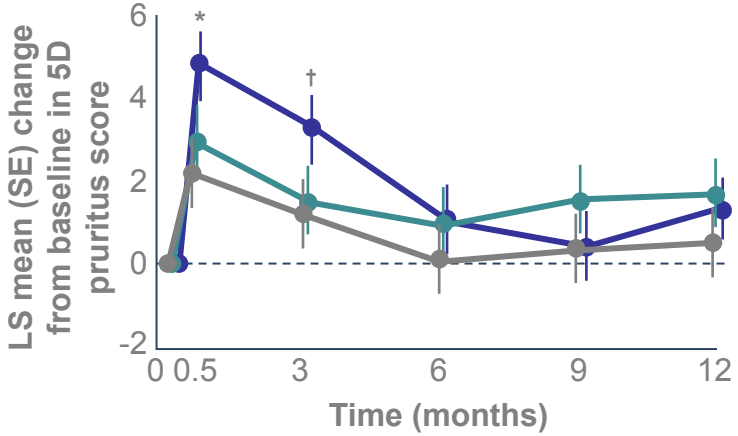
1. OCALIVA® (obeticholic acid). Summary of Product Characteristics, 2016; 2. Nevens F, *et al. N Engl J Med* 2016;375:631–43.

Obeticholic acid: Change in pruritus scores

Placebo + UDCA (n=73) | Obeticholic acid titration + UDCA (n=70) | Obeticholic acid 10 mg + UDCA (n=73)







Discontinuation due to pruritus:

- 10 mg: 10%
- 5–10 mg: 1%
- Placebo: 0%

*p<0.001; †p<0.01; ‡p<0.05 vs placebo. VAS of 0 (no pruritus) to 100 (severe pruritus).
UDCA, ursodeoxycholic acid; VAS, Visual Analogue Scale.
Nevens F, *et al. N Engl J Med* 2016;375:631–43 (supplementary appendix).

Conclusions

- There is an emerging landscape of new treatment options to address the needs of PBC patients with inadequate response to UDCA[1–4]
- After 15 years of UDCA treatment, 15% of patients still develop major hepatic complications[5]
- In the POISE study, obeticholic acid improved cholestasis in ~50% of patients who were unresponsive or intolerant to UDCA[6]
- Titrating the dose of obeticholic acid from 5 mg and to 10 mg can help to manage pruritus[7]

PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. Beuers U, *et al. J Hepatol* 2015;62:S25–37; 2. Mayo MJ, *et al. Hepatology* 2015;62:263A–264A; 3. Hosonuma K, *et al. Am J Gastroenterol* 2015;110:423–31; 4. Pellicciari R, *et al. J Med Chem* 2002;45:3569–72; 5. Harms MH. Paper submitted; 6. Nevens F, *et al. N Engl J Med* 2016;375:631–43; 7. OCALIVA® (obeticholic acid). Summary of Product Characteristics, 2016.