Lead team presentation Obeticholic acid for treating primary biliary cirrhosis – STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

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Key decision points

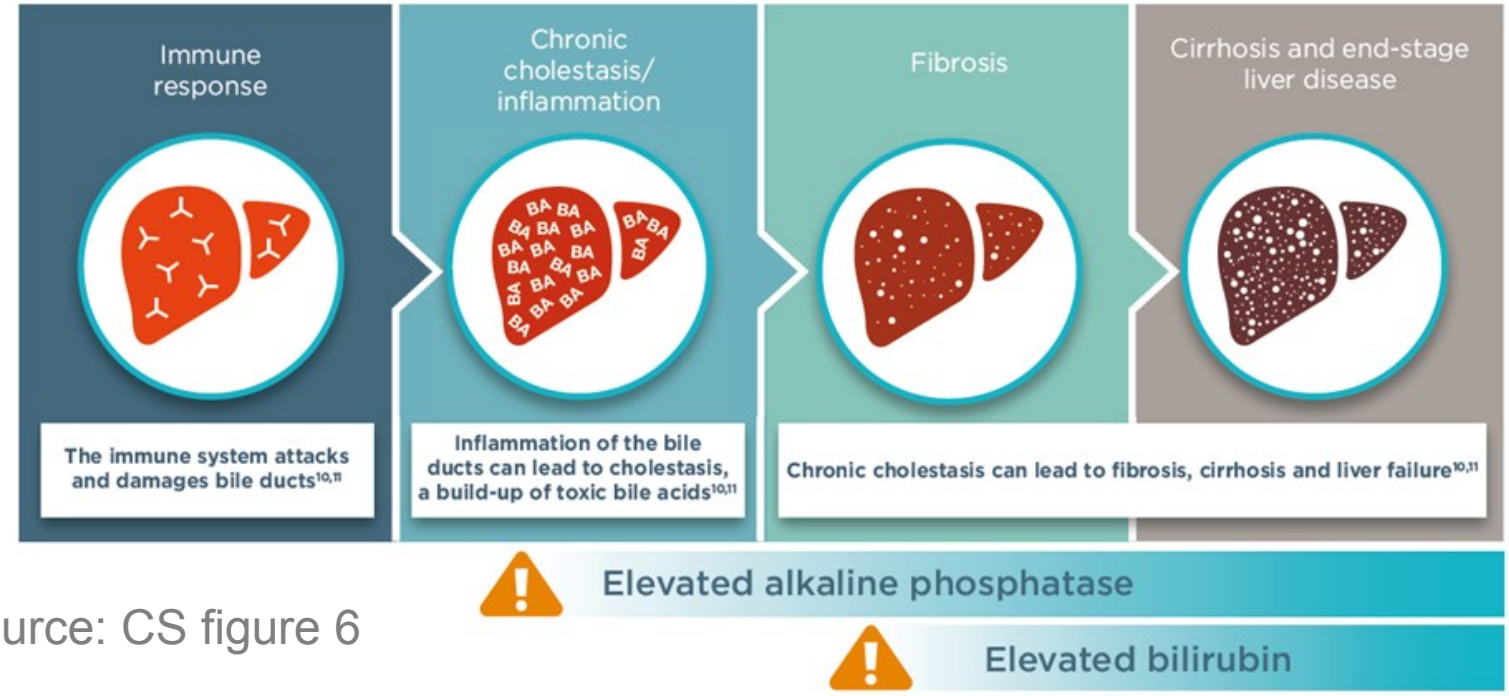
- Is there unmet clinical need?
- What is standard of care for people intolerant to/ have inadequate response to ursodeoxycholic acid (UCDA)?
- Are fibrates relevant comparators?
- What is the natural history of people with low alkaline phosphatase (ALP)? Can ALP be maintained at this level and will it prevent progression of primary biliary cirrhosis?
- How generalisable is the clinical trial in terms of
  - the proportion of people with moderate and severe primary biliary cirrhosis?
  - the proportion of people on obeticholic acid (OCA) monotherapy (n=11)
  - the value of the composite primary outcome in clinical practice (is there a strong enough relationship between the surrogate and improved long term liver outcomes)?
- How is obeticholic acid used in clinical practice (is it titrated)?
- How severe is the pruritus associated with obeticholic acid?
- Utility values for PMB/Liver health states – appropriate?

Primary biliary cirrhosis (PBC)

- Also known as primary biliary cholangitis is rare, progressive, autoimmune, non-viral disease of the liver that gradually destroys the interlobular bile ducts. This causes accumulation of cytotoxic bile acids in the liver, which leads to inflammation, liver fibrosis, cirrhosis, and ultimately liver failure.
- Estimated prevalence in the UK is ~ 3.9 per 10,000 population, equating to ~ 19,175 people in England.
- Incidence is 0.58 per 10,000 population.
- ~ 90% of people with the condition are women, and age of diagnosis is typically between 30 and 65 years
- ~ 60–80% of patients are asymptomatic at diagnosis. The diagnosis in asymptomatic patients is usually established after the chance finding of an elevated ALP level during the course of an unrelated illness.

PBC progression and association with alkaline phosphatase and total bilirubin level

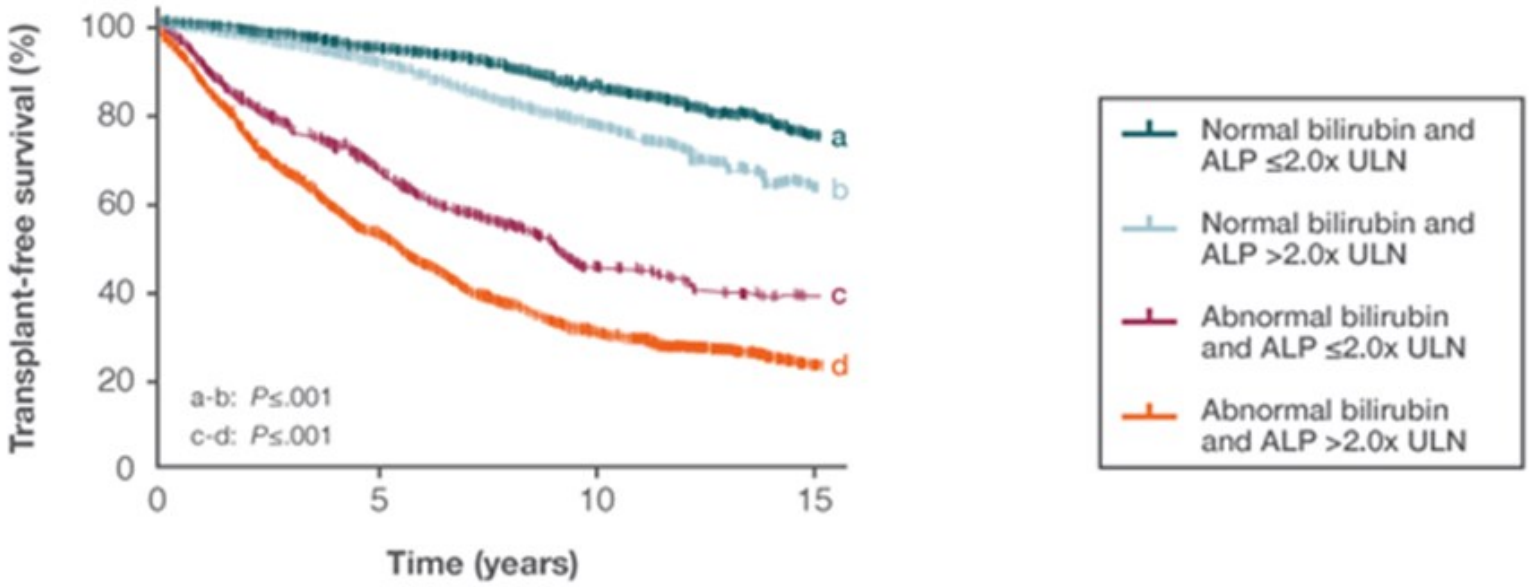
- The presence of anti-mitochondrial antibody and elevated alkaline phosphatase levels are two early characteristic markers of PBC.
- It is important to treat patients when their ALP levels >1.67x ULN, equivalent to 200 U/L.
- An increase in serum bilirubin is detected only when significant liver damage has occurred, with a sharp increase occurring in the terminal phase. A rise in bilirubin, even within the normal range, is a significant change in the course of the disease



Source: CS figure 6

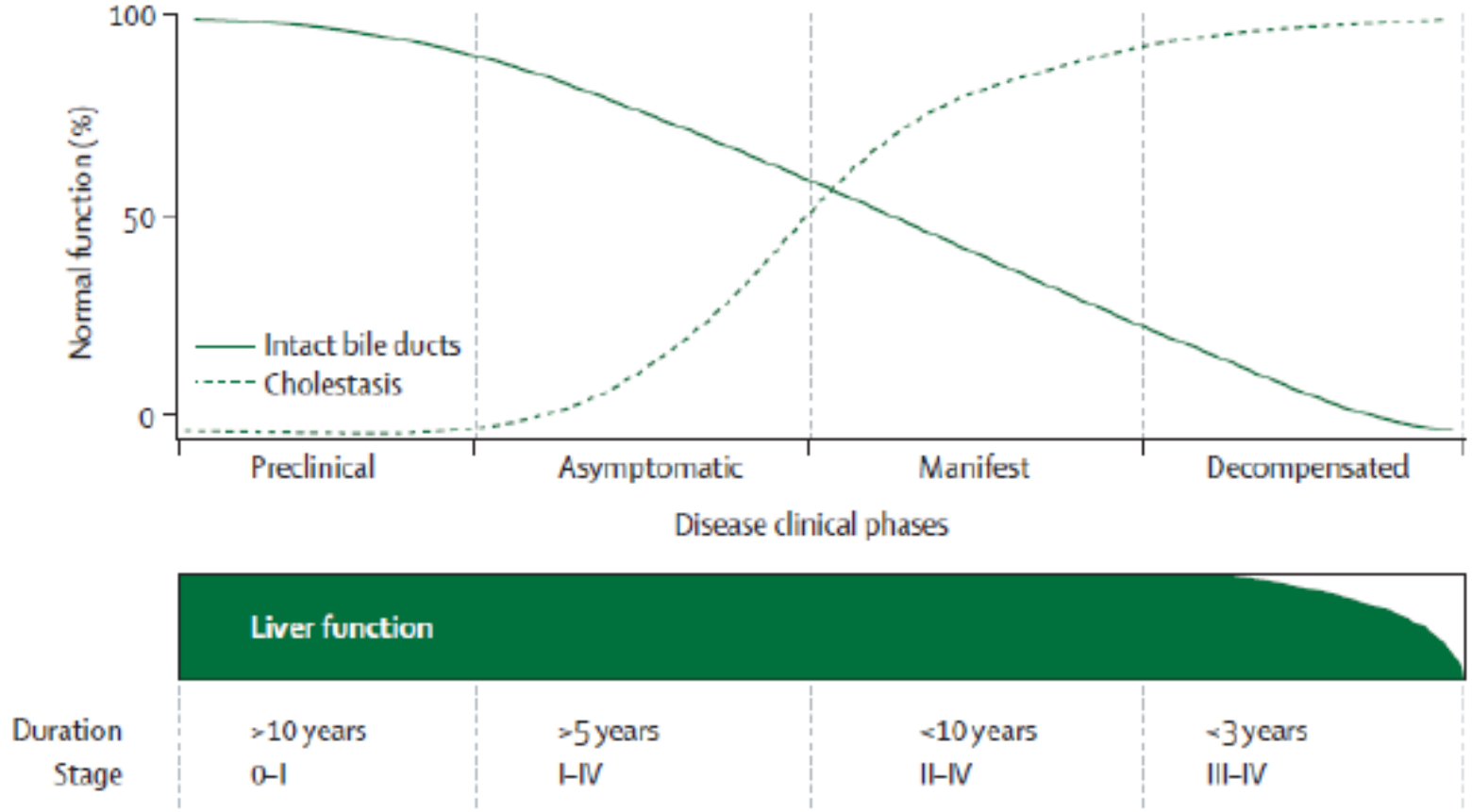
ALP and bilirubin level correlation with death and liver transplantation

- The company stated that serum ALP along with bilirubin are used to manage patients, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes.



Source: CS figure 7, p.35

Clinical phases of PBC: ductopenia and cholestasis



Source: CS figure 5, p.34

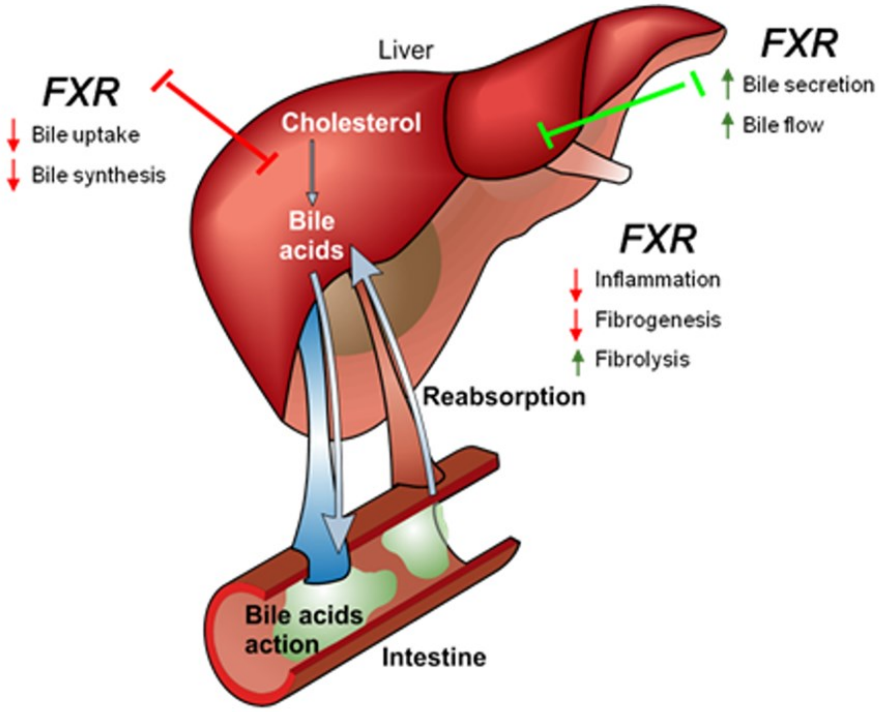
Current management

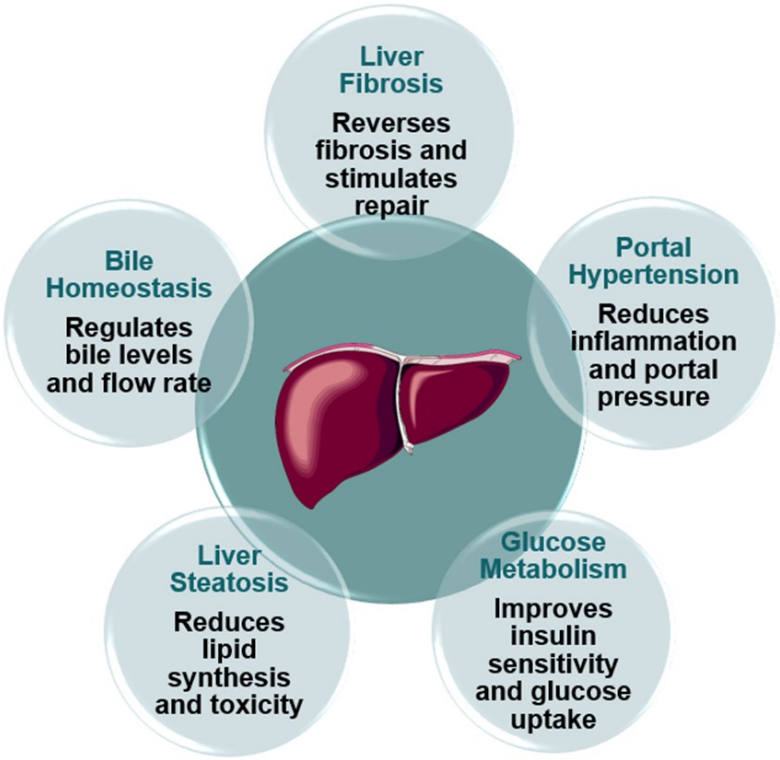
- First choice treatment: ursodeoxycholic acid (UDCA)
- Inadequate response to UDCA in up to 70% of people
- For people who are unable to tolerate, or whose disease responds inadequately to, UDCA – no licensed or effective treatments
- Immunosuppressive therapy no longer used for primary biliary cirrhosis. No benefit, severe side effects, not recommended in BSG/UK-PBC draft guidelines and the EASL guidelines.
- Liver transplant is an option only for people with end stage liver disease or decompensated cirrhosis (10% of these people have disease recurrence)

Obeticholic acid (OCA)

Conditional marketing authorisation	Granted on 12 December 2016
	“primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA”
	Conditional on follow up studies to demonstrate clinical benefits of reduced alkaline phosphatase and bilirubin levels e.g. delayed liver fibrosis, cirrhosis, liver transplant, death
Administration & dosage	Oral tablet (5 mg or 10 mg) Start on 5 mg/day, increase to 10 mg/day after 6 months
Duration of treatment	As long as person continues to benefit (dose reduced/interrupted for severe intolerability due to pruritis)
Cost	£2,384.04 for 30 tablets (list price) → £29,005.78/year A confidential patient access scheme has been approved

OCA mechanism of action





- OCA is farnesoid X receptor (FXR) agonist which:
  - ↓ bile acid synthesis
  - ↓ uptake and ↑ secretion of bile acids in and out of liver cells
  - mediates anti-inflammatory and anti-fibrotic pathways

Source: CS figures 1 and 2

Patient perspective - the PBC Foundation

- The diagnosis of an incurable, progressive disease, particularly one with such a foreboding outline can lead to an insurmountable emotional burden.
- Living with PBC has been described as “living on an emotional and physical rollercoaster”.
- One in three PBC sufferers experience depression.
- Symptoms vary from week to week and day to day.
- The main symptoms include: chronic fatigue (with the linked symptom of cognitive impairment), pruritus, joint/muscle/bone pain, and nausea
- The symptoms, alone, can have an enormously detrimental effect on quality of life.
- Many patients do not respond satisfactorily to UDCA, and face “life without hope”.
- Patients and carers are fearful of liver transplantation.
- Liver transplantation is not curative for PBC.

Patient perspective - the PBC Foundation

- Patients perceive there to be a lack of knowledge and understanding within medical communities, particularly in primary care and district hospital levels.
- As OCA is the first new therapy for PBC in over 20 years, it may provide opportunity for much needed education of medics about the PBC.
- Currently there is no second line therapy for PBC
- While complications of pruritus are associated with OCA, anecdotal evidence suggests that “itch normalises within a short timeframe”.
- OCA’s benefits include:
  - Addresses the unmet need of those patients who do not respond to the only other medication available for PBC;
  - Fixed dosage (not dependant on patient’s weight);
  - Simplifies prescription and daily intake of medication:
  - Prolonged life expectancy
  - Improved quality of life (for patients and carers);
  - Less need for liver transplantation.

Decision problem (final scope)

Population	People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid (UDCA)
Intervention	OCA alone or in combination with UDCA
Comparators	For people whose disease has an inadequate response to UDCA: • UDCA alone or in combination with fibrates For people who are unable to tolerate UDCA: • Fibrates • No additional treatment
Outcomes	• Mortality • Liver function based on markers of liver biochemistry • Symptoms, including pruritus, fatigue and abdominal pain • Time to liver transplantation • Primary biliary cirrhosis related events, including ascites, varices, encephalopathy and HCC • Adverse effects of treatment • Health-related quality of life

Company deviations from the scope (1): comparators

Company submission did not include fibrates, with the rationale that fibrates:

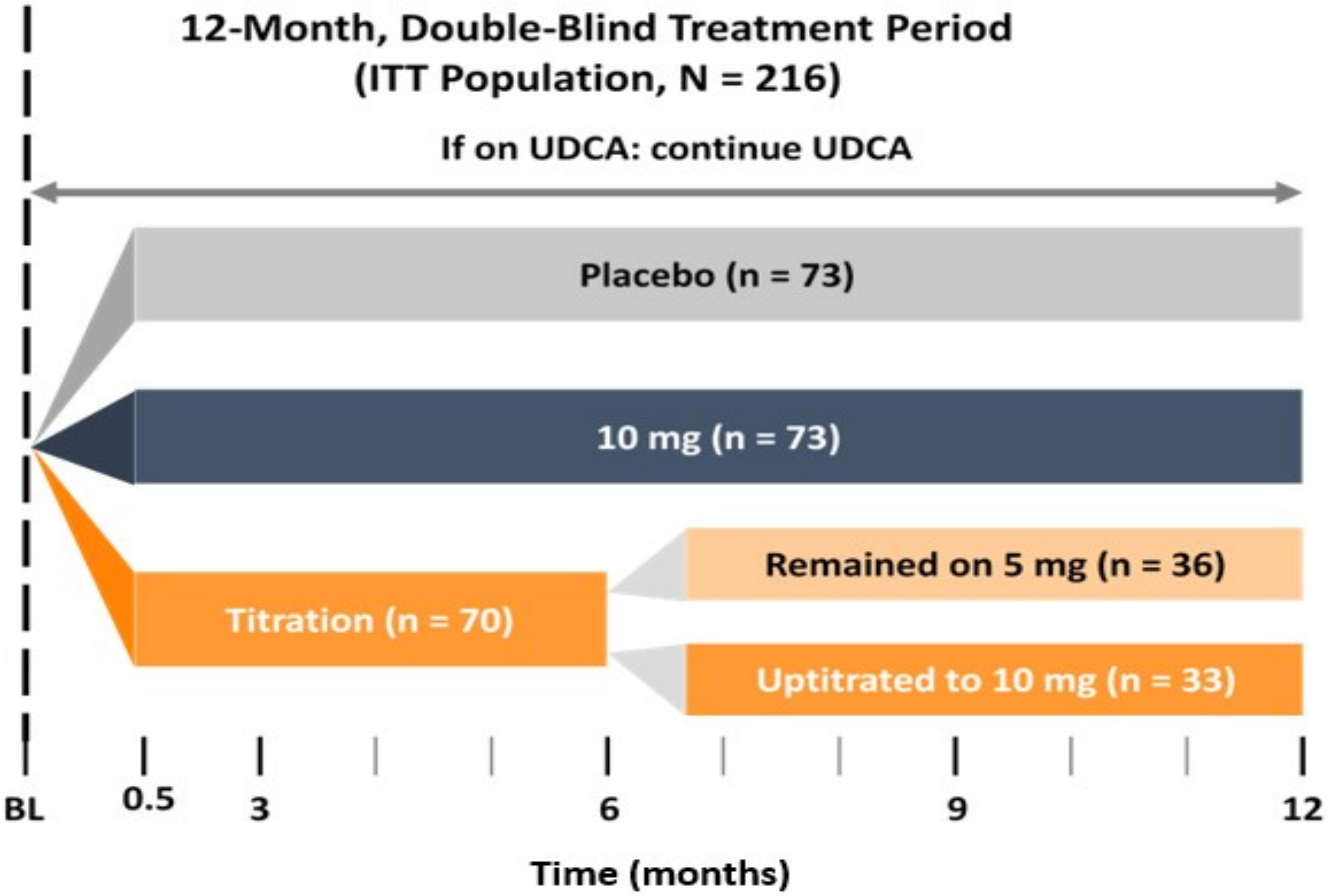
- do not have a marketing authorisation for primary biliary cirrhosis in the UK
- not standard of care
- contraindicated in primary biliary cirrhosis
- rarely used: XX% of patients in the UK-PBC cohort (XX/2,245) have ever taken fibrates for any condition (not necessarily for PBC)
- do not have proven efficacy; there only a limited number of studies of fibrates in primary biliary cirrhosis, with the following challenges:
  - small patient numbers
  - all except 1 study was conducted in Japanese patients
  - poor trial quality and high risk of bias
  - significant safety concerns

Clinical effectiveness evidence

POISE trial

- Phase 3, randomised double-blind, placebo-controlled, parallel group trial, n=216. Stratified randomisation according to:
  - higher risk of developing clinical outcomes
  - intolerance to UDCA
  - presence or absence of biochemical response to UDCA treatment
- 59 sites in 13 countries including 7 sites in England and 2 sites in Scotland
- Intervention: OCA 10 mg, OCA titration, placebo with or without UDCA
- Primary outcomes:
  - percentage of participants at 12 month achieving the composite endpoint: ALP <1.67x ULN, **and** total bilirubin ≤ULN, **and** ALP decrease ≥15% from baseline
- Secondary outcomes:
  - percentage of patients having the primary endpoint in the OCA titration group at month 12,
  - percentage of patients reaching the endpoint at week 2, month 3, month 6 and month 9, and comparing the 10 mg OCA fixed dose group with the OCA titration group at month 6.
- The primary variable for the long-term safety extension phase was the percentage of patients having the composite endpoint based on previous treatment in the double-blind phase

Design of the POISE trial



Source: CS p.49

BL – baseline, UDCA – ursodeoxycolic acid

POISE baseline characteristics

- 81% of patients were younger than 65 years old.
- 91% female
- 11 patients were UDCA intolerant

	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg (n=73)
Mean age, years (SD)	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)
BMI<30 kg/m^2	79%	83%	84%
Pre-treatment liver biopsy	10%	19%	12%
UDCA use at baseline	93%	93%	92%
Baseline liver parameters, ITT population			
ALP >3x ULN	32%	27%	27%
Total bilirubin >ULN	10%	6%	10%

ALP, alkaline phosphatase; BMI, body mass index; OCA, obeticholic acid; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

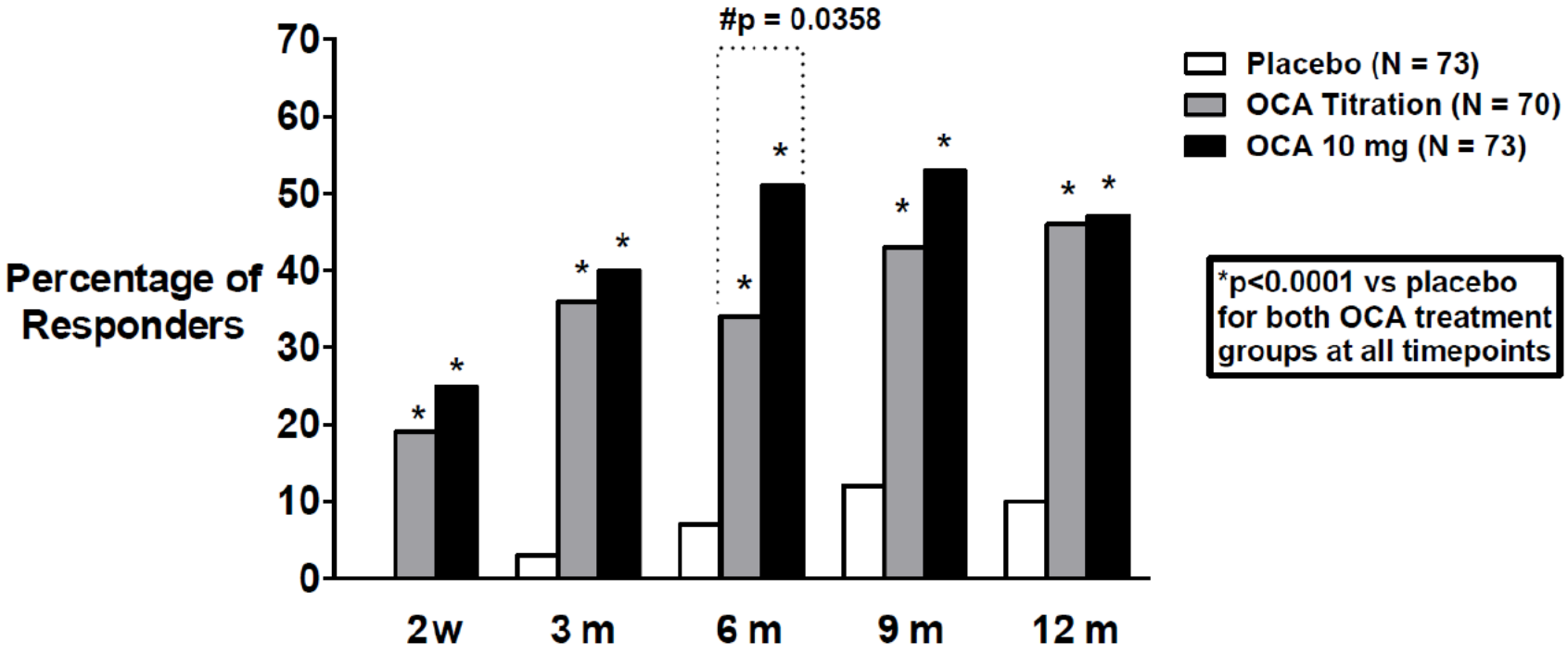
Source: Tables 20, 22 CS.

POISE results

Primary outcomes	**Responders at Month 12**	
	Placebo (n=73)	10%
	10 mg OCA (n=73)	47%
	Titration OCA (n=70)	46%
	Titration subgroup	
	Remained at 5 mg OCA for 12 months (n=36)	53%
	Titrated to 10 mg OCA at Month 6 (n=33)	39%
Secondary outcomes	**ALP reduction from baseline ≥40% at Month 12**	
	Placebo (n=73)	1%
	10 mg OCA (n=73)	34%
	Titration OCA (n=70)	30%
	Mean total bilirubin levels at Month 12	
	Placebo (n=73)	13.2 (SE 1.0)
	10 mg OCA (n=73)	9.7 (SE 0,6)
	Titration OCA (n=70)	9.9 (SE 0.6)

Source: CS table 23 and ERG report p. 49

POISE results: responders

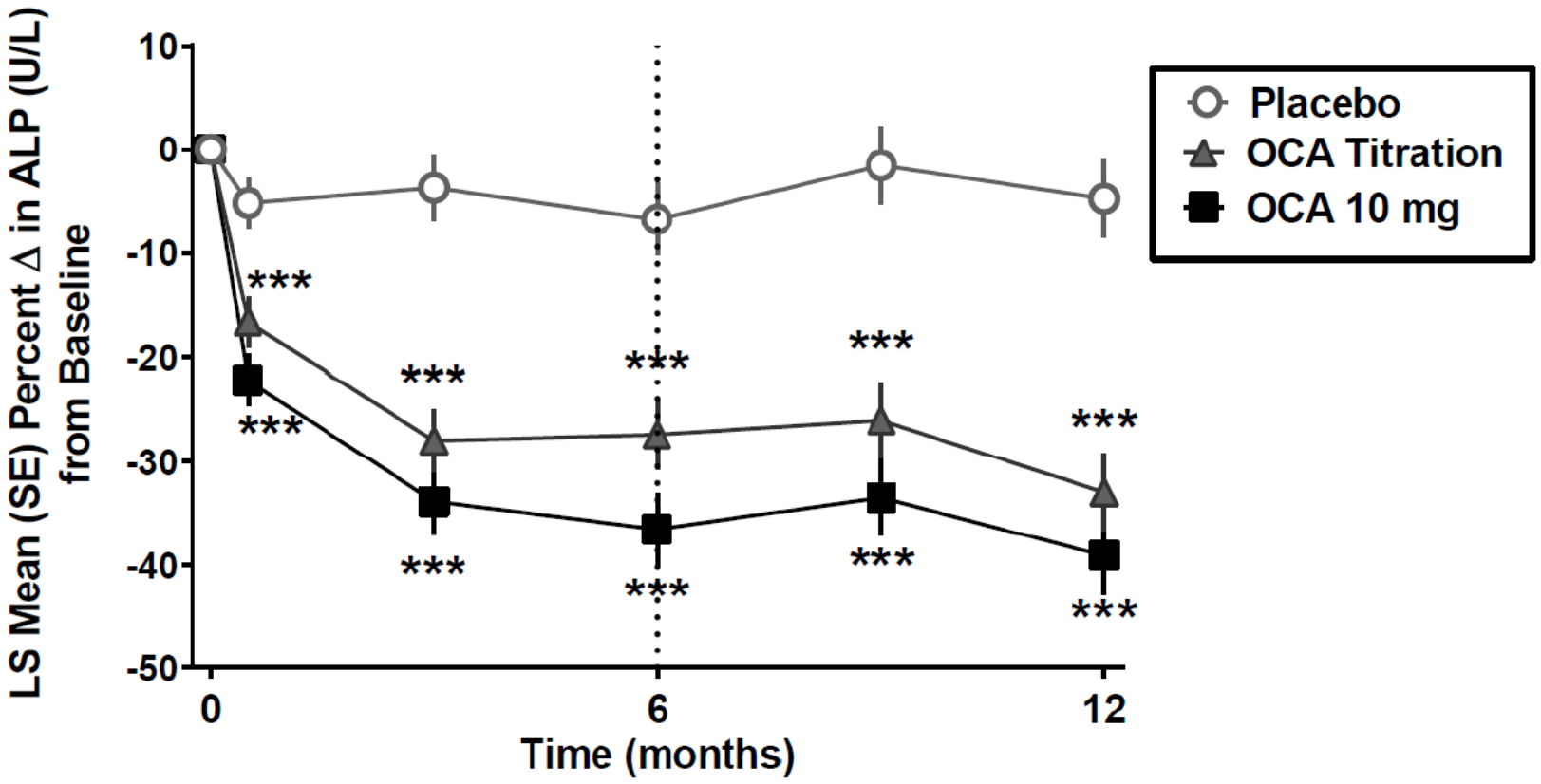


Abbreviations: OCA, obeticholic acid.
* p-value for treatment group versus placebo; # p-value for the between treatment group comparison at Month 6 of OCA titration (5 mg) and OCA 10 mg. P-values obtained using Cochran-Mantel-Haenszel tests stratified by randomization strata factor. Missing values were considered a non-response.

Source: CS fig 12

POISE results: ALP

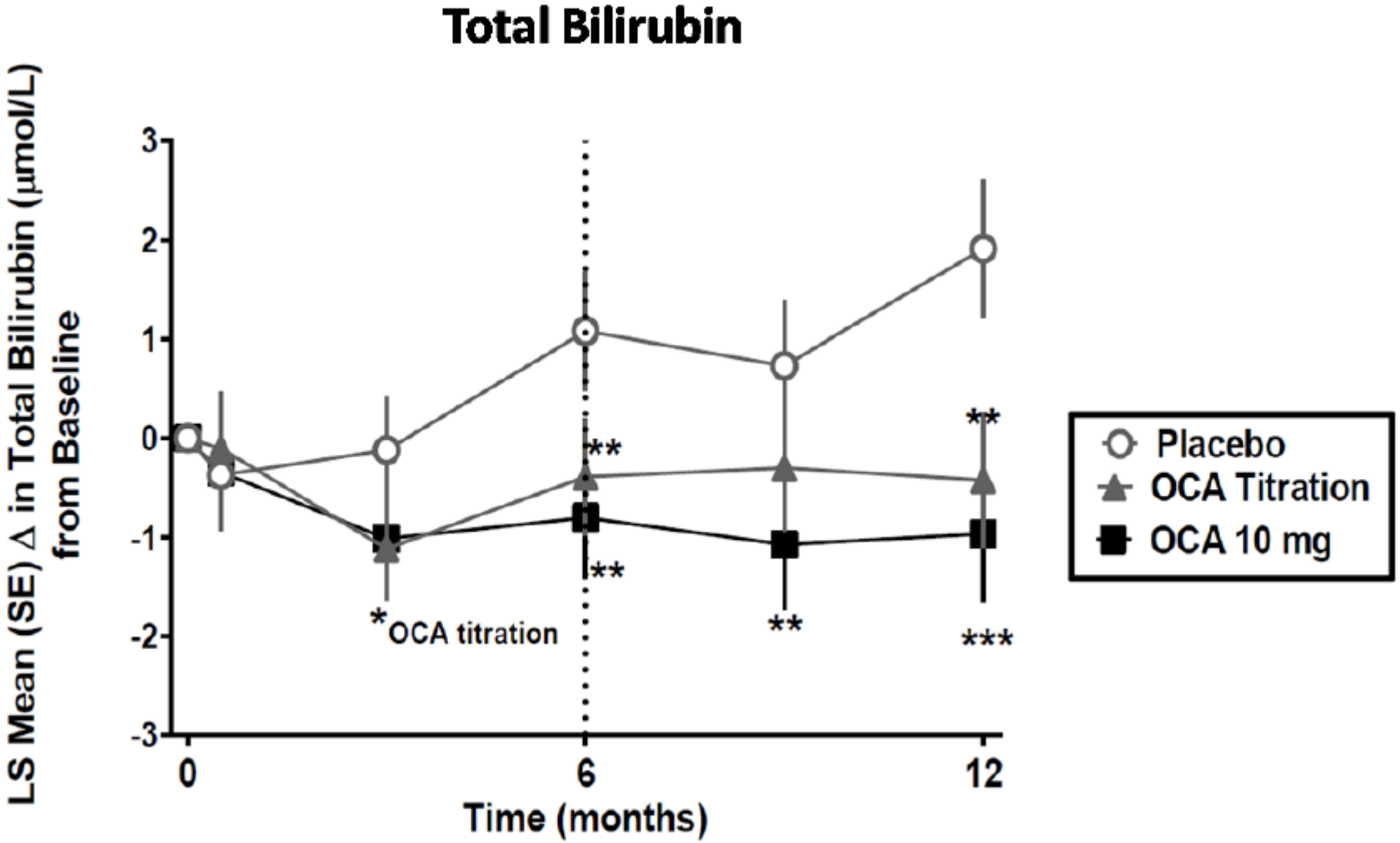
Figure 17: Change in ALP from baseline over time: ITT population



Abbreviations: ALP, alkaline phosphatase; ITT, intention-to-treat; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
*** p<0.0001 vs placebo.

Source: CS figure 17

POISE results: Bilirubin



Abbreviations: ANCOVA, analysis of covariance; LS, least squares; OCA, obeticholic acid; SE, standard error. *p<0.05, **p<0.01, ***p<0.0001 vs placebo; p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Source: CS figure 18

Adverse events

Participants, n (%)	Placebo n=73	OCA titration n=70	OCA 10 mg n=73
Any treatment-related adverse events	38 (52)	42 (60)	54 (74)
Any serious adverse events	3 (4)	11 (16)	8 (11)
Pruritus	27 (37)	35 (50)	48 (66)
Discontinuation due to pruritus	0 (0)	1 (1)	7 (10)
Number of deaths	0 (0)	1 (1)	0 (0)

Source: CS table 37

ERG comments

- No trials comparing OCA with fibrates were identified.
- The group receiving OCA as monotherapy is underrepresented in the POISE trial (11 patients).
- The majority of patients in POISE appeared to be at an earlier stage of disease so the effects on those with more advanced disease are less clear.
- The POISE trial only examined surrogate outcomes; OCA showed positive effects on surrogate endpoints, and there is some evidence that surrogate endpoints are related to relevant outcomes. However, the size of the relationship is unclear.
- Two extension studies to POISE trial were not similar enough to be pooled with POISE trial. Clinical outcomes await the publication of the COBALT trial which is estimated to be in 2022.