EASL CONGRESS 2023
Vienna, Austria
21–24 June

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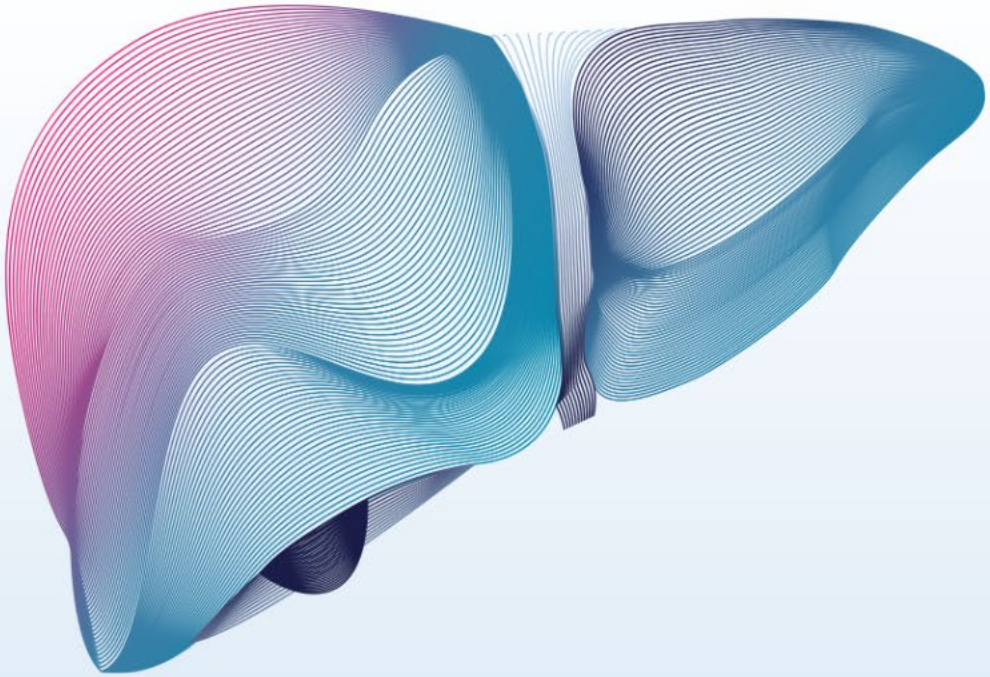

Results from a planned interim analysis of a randomized, double-blind, active-controlled trial evaluating the effects of obeticholic acid and bezafibrate on serum biomarkers in primary biliary cholangitis

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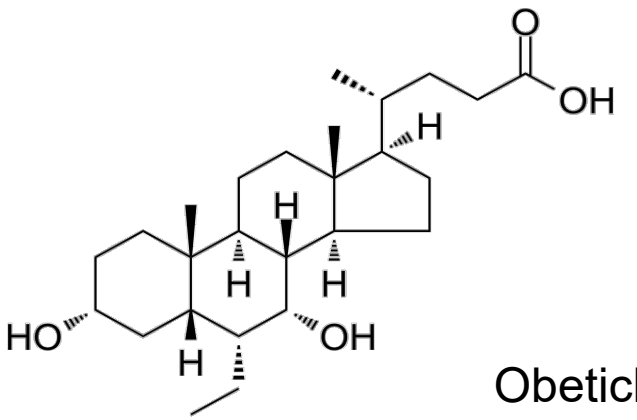
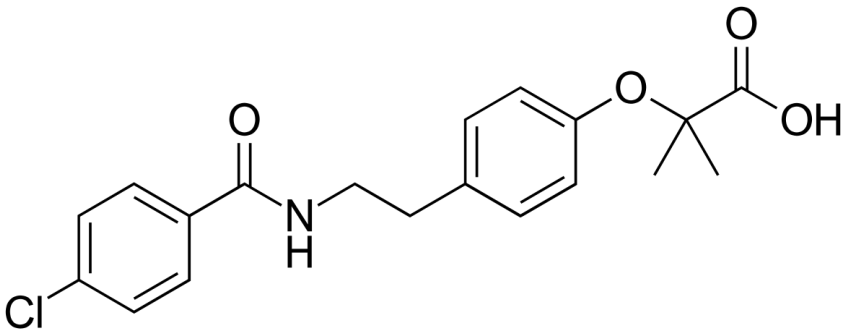
Obeticholic Acid and Bezafibrate for the Treatment of Primary Biliary Cholangitis

Obeticholic acid (OCA), a potent farnesoid X receptor agonist, is approved as a second-line treatment for primary biliary cholangitis (PBC) in those patients with an inadequate response or intolerance to ursodeoxycholic acid (UDCA)[1]



Obeticholic Acid

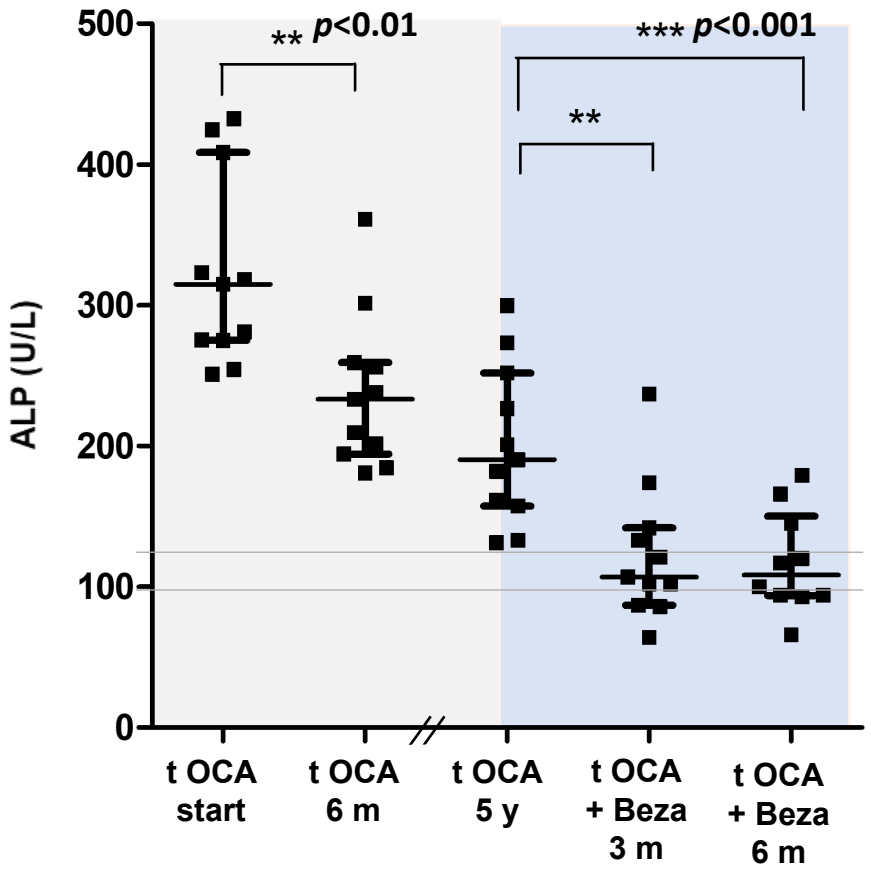
Bezafibrate (BZF), a pan-peroxisome proliferator–activated receptor agonist, benefits patients with PBC who have an inadequate response to UDCA[2]



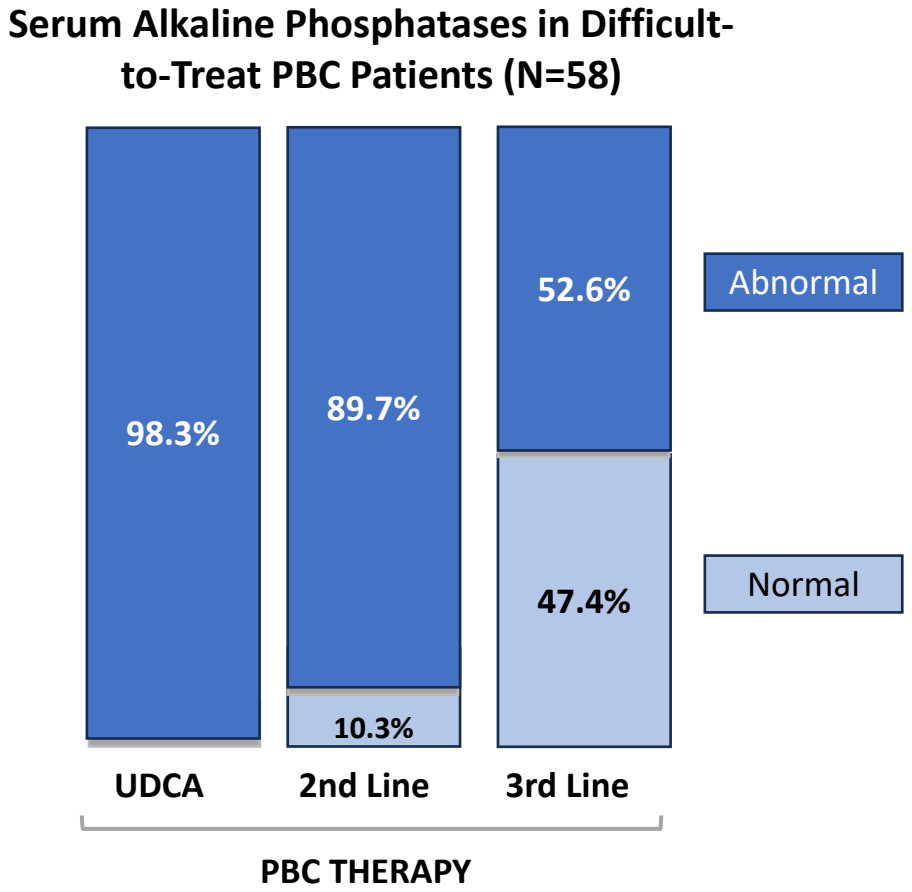
Bezafibrate

1. Nevens F, et al. *N Engl J Med.* 2016. 2. Corpechot C, et al. *N Engl J Med.* 2018.

Preliminary Data Showed Promise With the Combination of Obeticholic Acid and Bezafibrate in Patients With Poor Response to UDCA



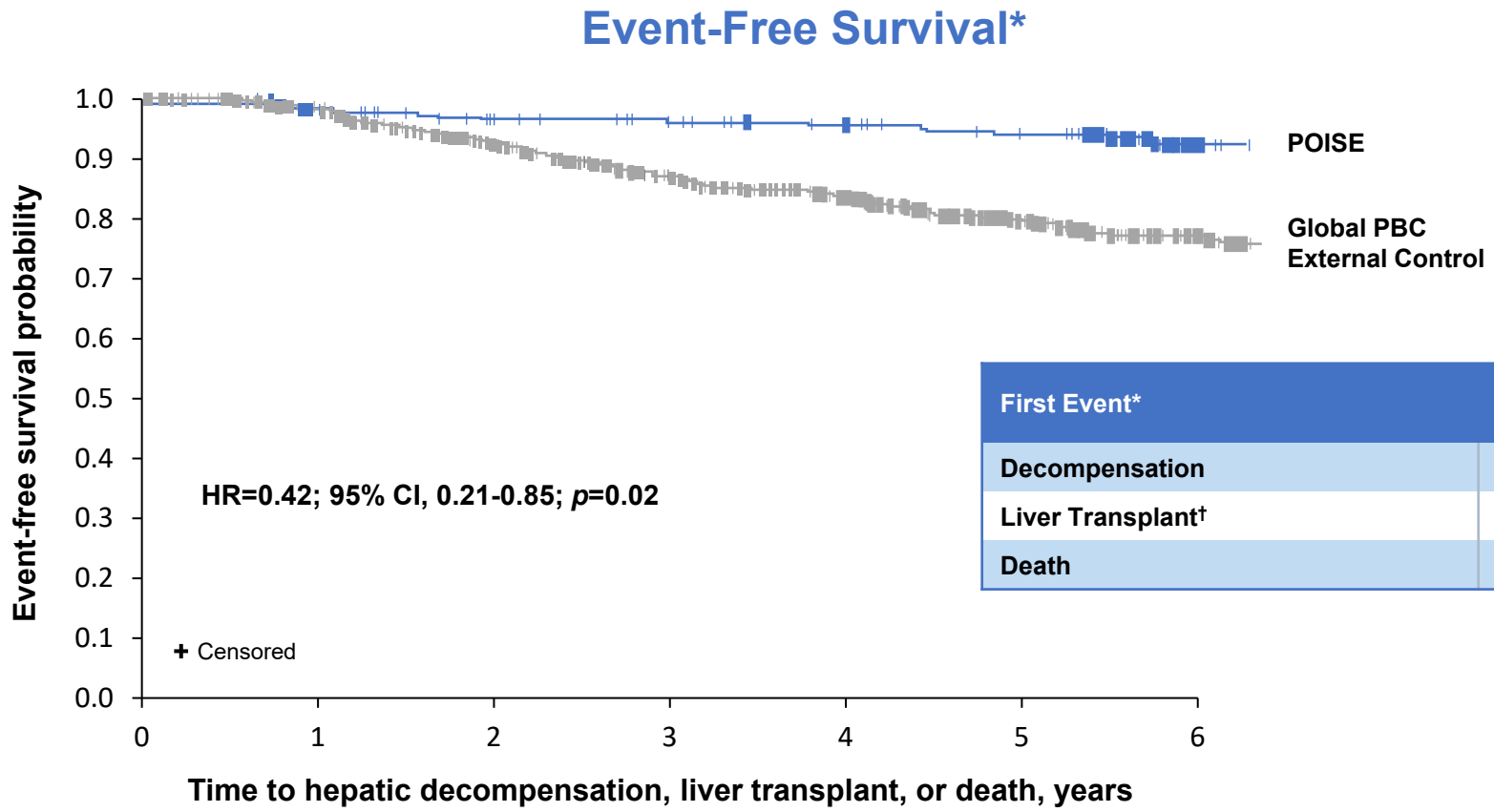
Smets L, et al. Oral Presentation EASL 2019. *Hepatology*. 2021.



Soret PA, et al. *Aliment Pharmacol Ther*. 2021.

Abbreviations: ALP, alkaline phosphatase; Beza, bezafibrate; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

Event Free Survival Demonstrated for OCA in POISE LTSE Compared to External Controls



First Event*	POISE (n=16)	Global PBC (n=212)
Decompensation	12	126
Liver Transplant†	1	23
Death	3	63

*First occurrence of hepatic decompensation, liver transplant, or death; †Of the 2 patients with liver transplant in the primary outcomes analysis, 1 had hepatic decompensation before the transplant in the secondary outcomes analysis.
Murillo Perez CF et al. *Gastroenterology.* 2022.
Abbreviations: CI, confidence interval; HR, hazard ratio; LTSE, long-term safety extension; OCA, obeticholic acid; PBC, primary biliary cholangitis.

Dose-Range Exploration for the Fixed-Dose Combination of Obeticholic Acid and Bezafibrate

The global research program to date includes:

- Study 123: explored a range of doses of obeticholic acid and bezafibrate in healthy adult subjects using cross-over methodology
- Study 213: Phase 2 (n=~72 patients), predominantly in Europe
- Study 214: Phase 2 (n=62 patients), predominantly in the United States, Argentina, and Turkey

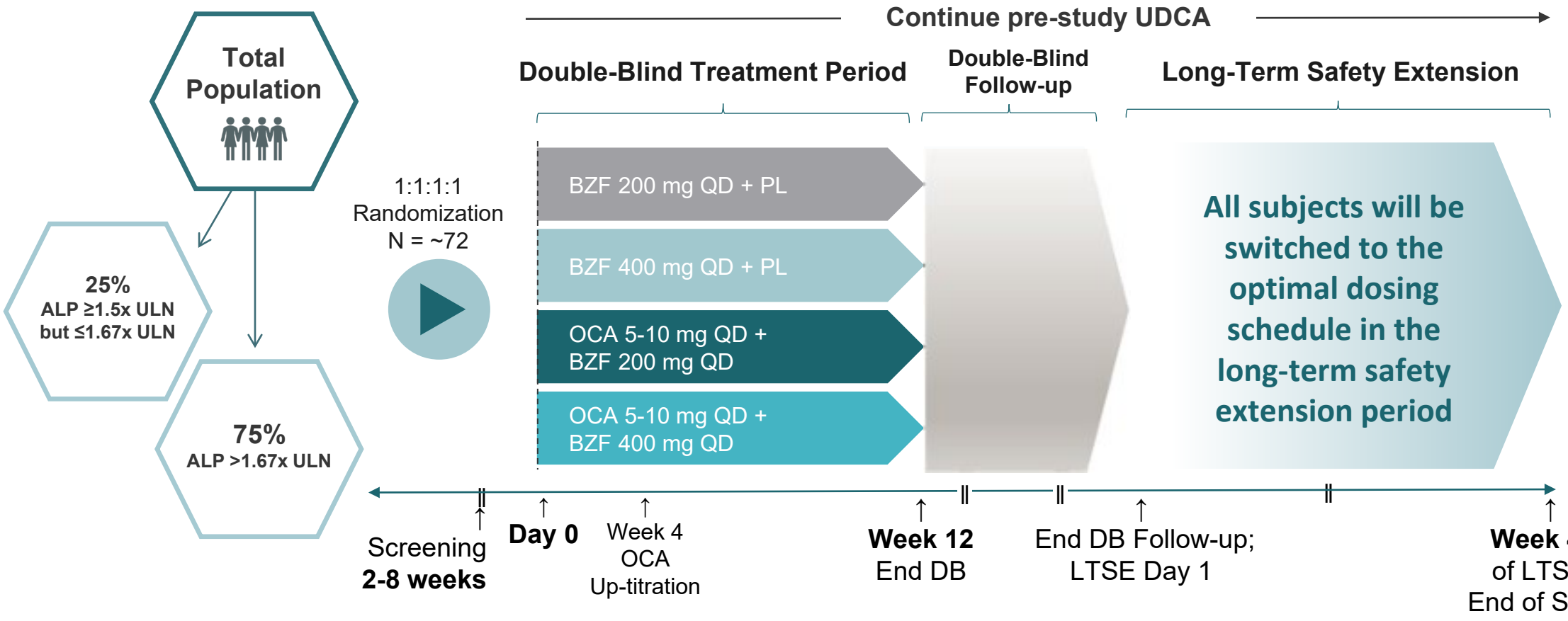
Today's presentation focuses on the planned 12-week interim analysis from the European 747-213 study

Study 213 Objective and Primary Endpoint

- The goal of this interim analysis of an ongoing phase 2 trial was to assess:
  - Improvements in five key serum biomarkers of cholestasis (ALP, GGT, total bilirubin, ALT, and AST) following treatment with BZF monotherapy or a combination of OCA and BZF
  - Safety and tolerability assessed by AEs and laboratory values
- The primary efficacy endpoint is *change in ALP from baseline to week 12*

Abbreviations: AEs, adverse events; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BZF, bezafibrate; GGT, gamma-glutamyl transferase; OCA, obeticholic acid.

Study 213 Design: Active Comparator



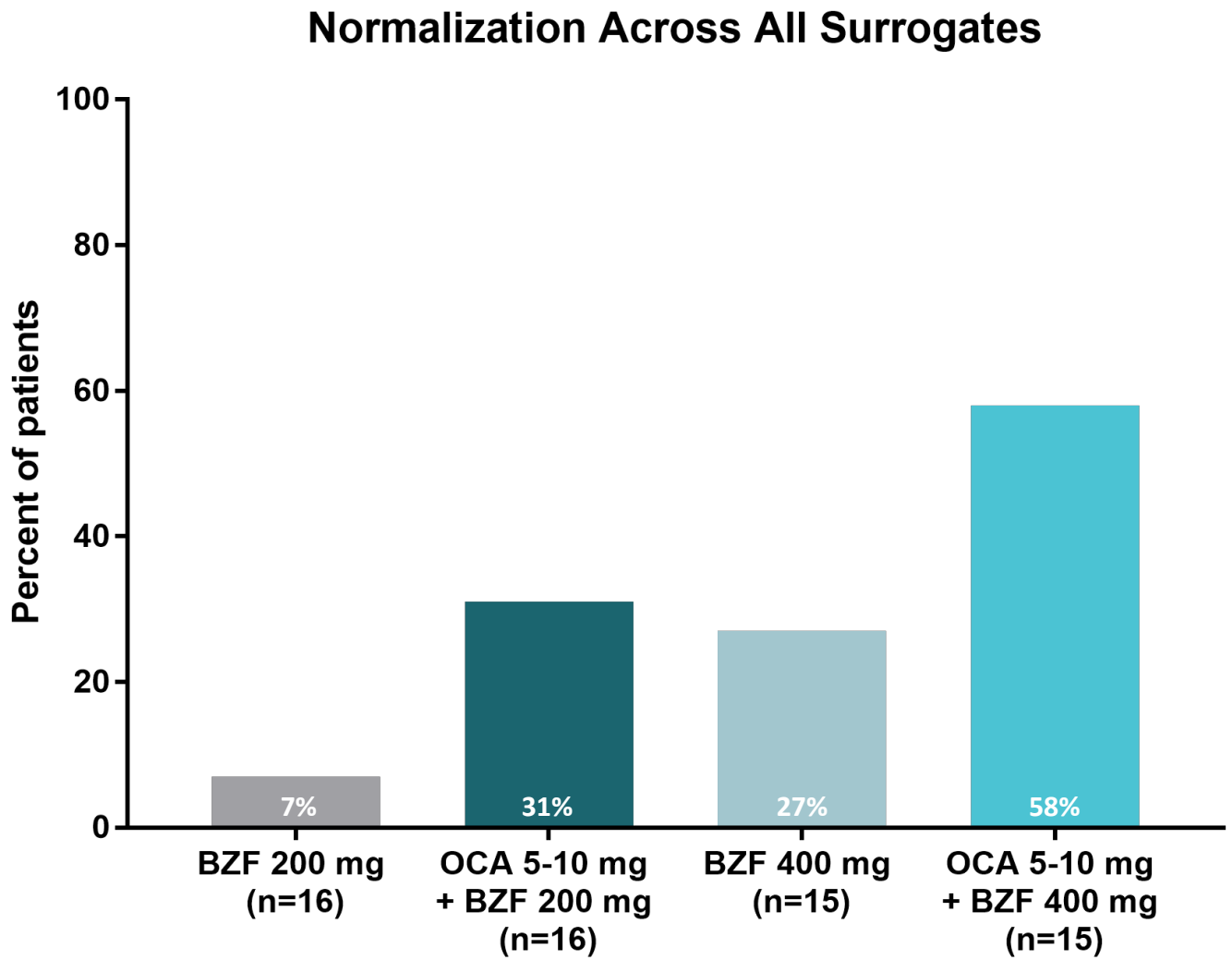
Abbreviations: ALP, alkaline phosphatase; BZF, bezafibrate; DB, double-blind; PL, placebo; LTSE, long-term safety extension; OCA, obeticholic acid; QD, daily; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Baseline Demographics and Clinical Characteristics

Parameters	BZF 200 mg (n=16) No. (%)	OCA 5-10 mg + BZF 200 mg (n=16) No. (%)	BZF 400 mg (n=15) No. (%)	OCA 5-10 mg + BZF 400 mg (n=15) No. (%)	Overall (N=62) No. (%)
Age, mean (SD), y	58 (7.78)	55.7 (6.57)	52.8 (8.79)	55.4 (8.88)	55.5 (8.05)
Sex, mean (SD)					
Male	2 (12.5)	2 (12.5)	1 (6.7)	0	5 (8.1)
Female	14 (87.5)	14 (87.5)	14 (93.3)	15 (100)	57 (91.9)
Race, mean (SD)					
White	14 (87.5)	14 (87.5)	14 (93.3)	14 (93.3)	56 (90.3)
Black or African American	0	0	0	0	0
Asian	1 (6.3)	0	0	0	1 (1.6)
UDCA treatment, mean (SD)					
Duration of UDCA in years	6.7 (4.33)	7.9 (7.28)	6.1 (4.23)	9.2 (8.26)	7.4 (6.23)
UDCA dose (mg/d)	721.9 (478.78)	625.1 (328.95)	653.4 (355.64)	742.9 (344.10)	684.5 (376.67)
Biomarker, mean (SD)					
ALP (U/L)	256 (70.64)	293.8 (190.08)	272.4 (98.77)	326.9 (152.11)	286.9 (135.53)
Bilirubin (mmol/L)	8.4 (4.51)	10.5 (4.86)	10.5 (4.36)	9.2 (4.48)	9.6 (4.54)
ALT (U/L)	50.7 (30.93)	50.4 (32.87)	43.2 (27.28)	51.9 (32.52)	49.1 (30.43)
AST (U/L)	42.8 (19.78)	47.9 (33.87)	36.5 (14.48)	43.5 (19.84)	42.8 (23.09)
GGT (U/L)	132.8 (96.28)	228.9 (199.57)	173.37 (146.31)	209.49 (160.76)	185.96 (155.94)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BZF, bezafibrate; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

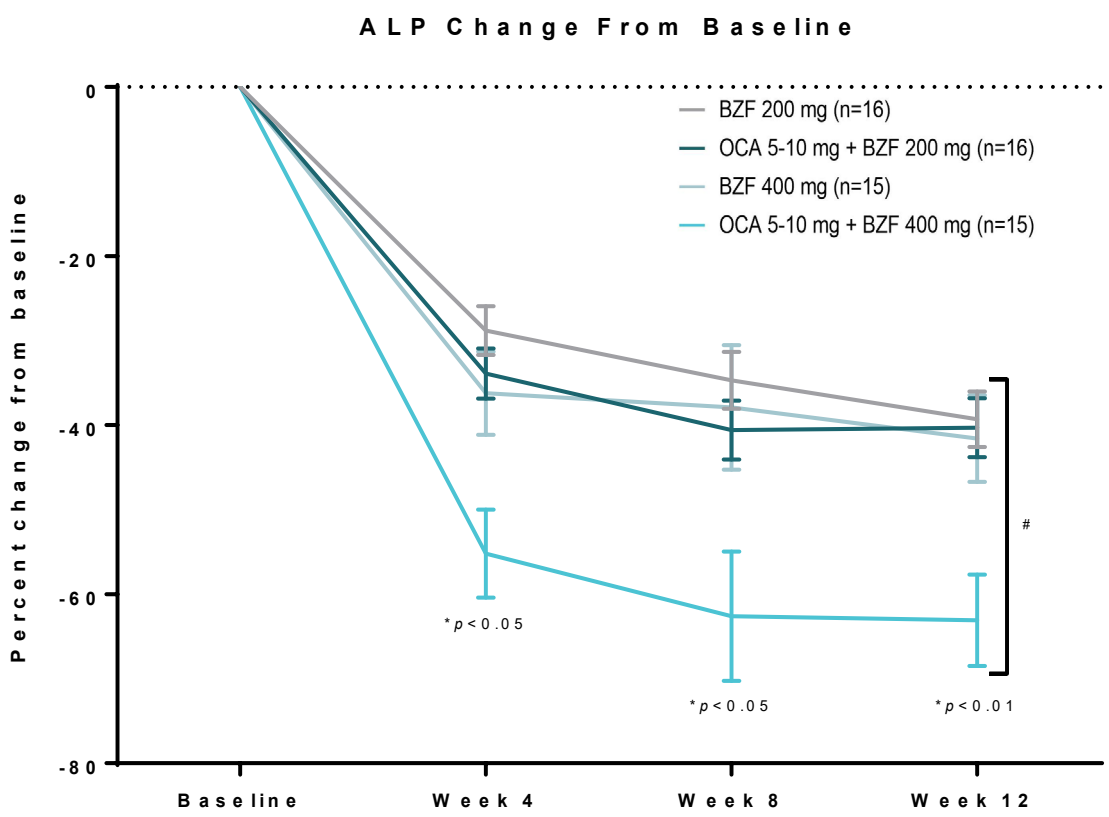
OCA 5-10 mg + BZF 400 mg Induced a Biochemical Remission in 58% of Subjects

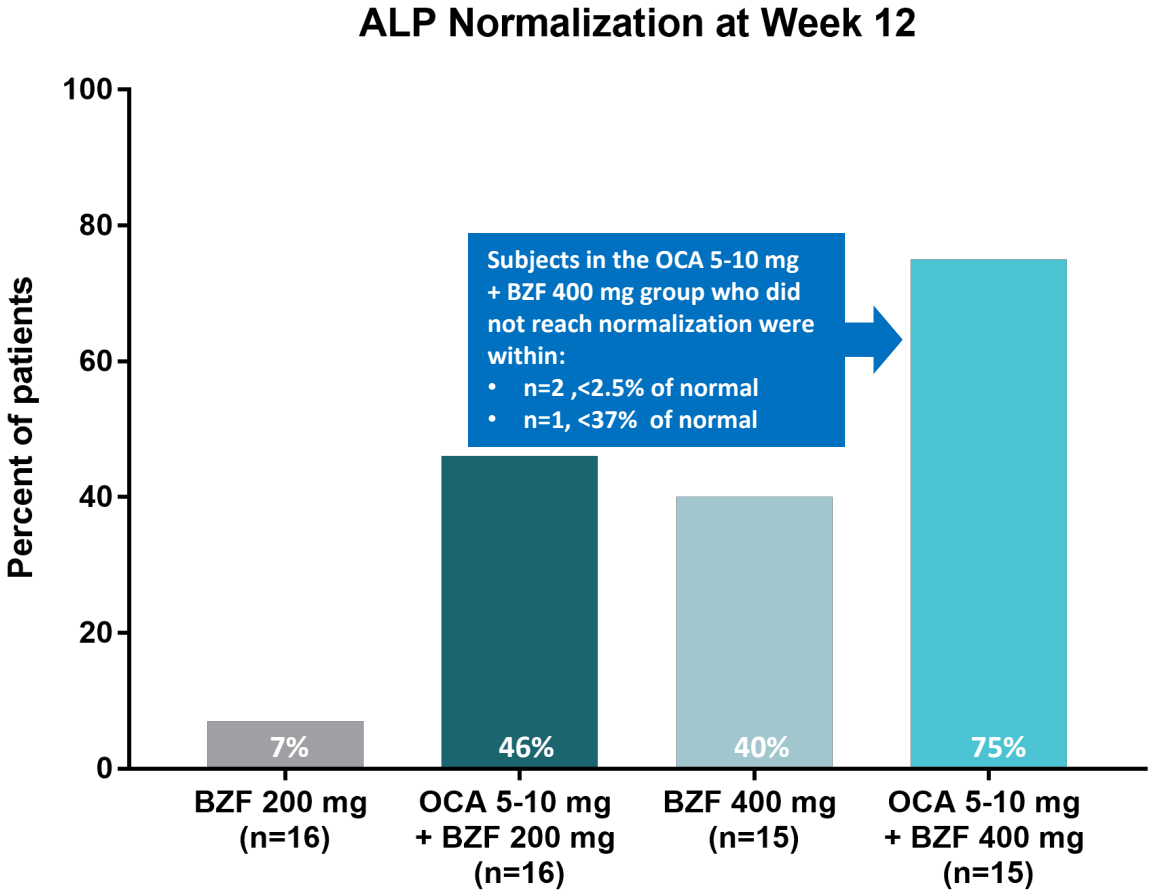


Biochemical remission:
ALP, GGT, ALT, AST
All ≤ULN
AND
Total bilirubin
≤0.6x ULN

Data are shown as LS mean values ± standard error of the mean.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BZF, bezafibrate; GGT, gamma-glutamyl transferase; LS, least-squares; OCA, obeticholic acid; ULN, upper limit of normal.

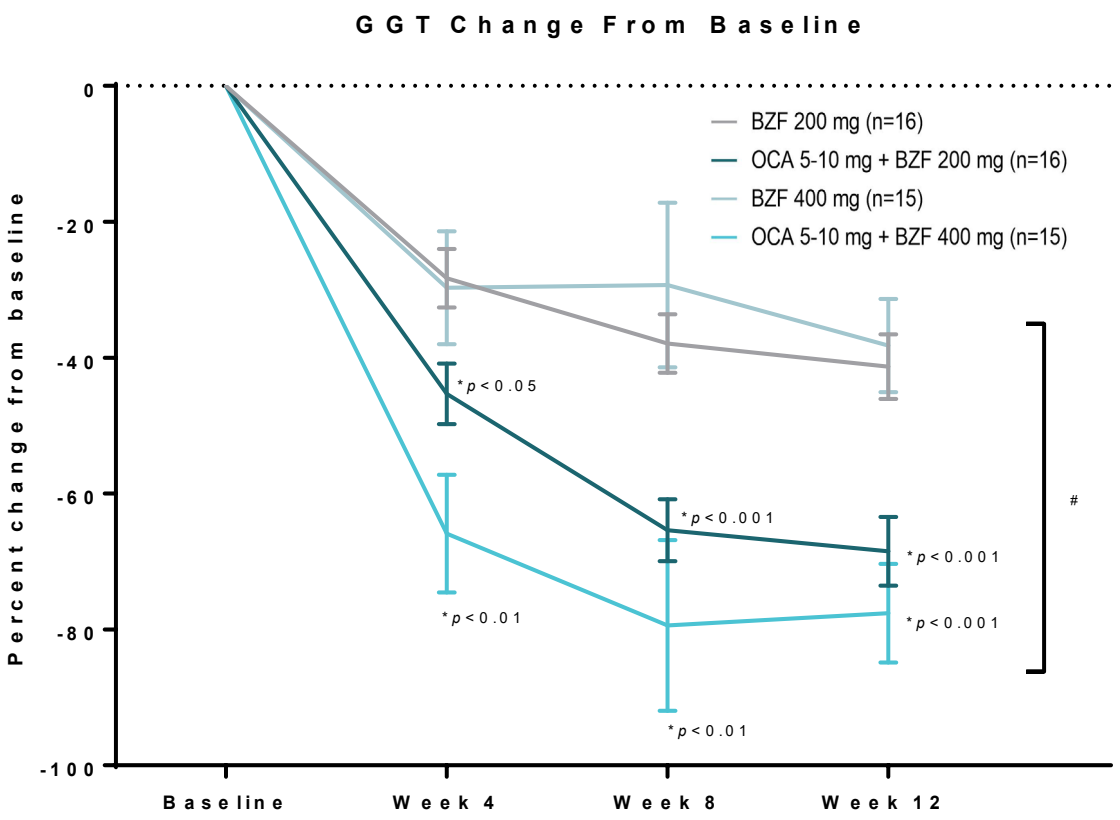
OCA 5-10 mg + BZF 400 mg Induced a Rapid and Greater Normalization of ALP Relative to BZF Through Week 12

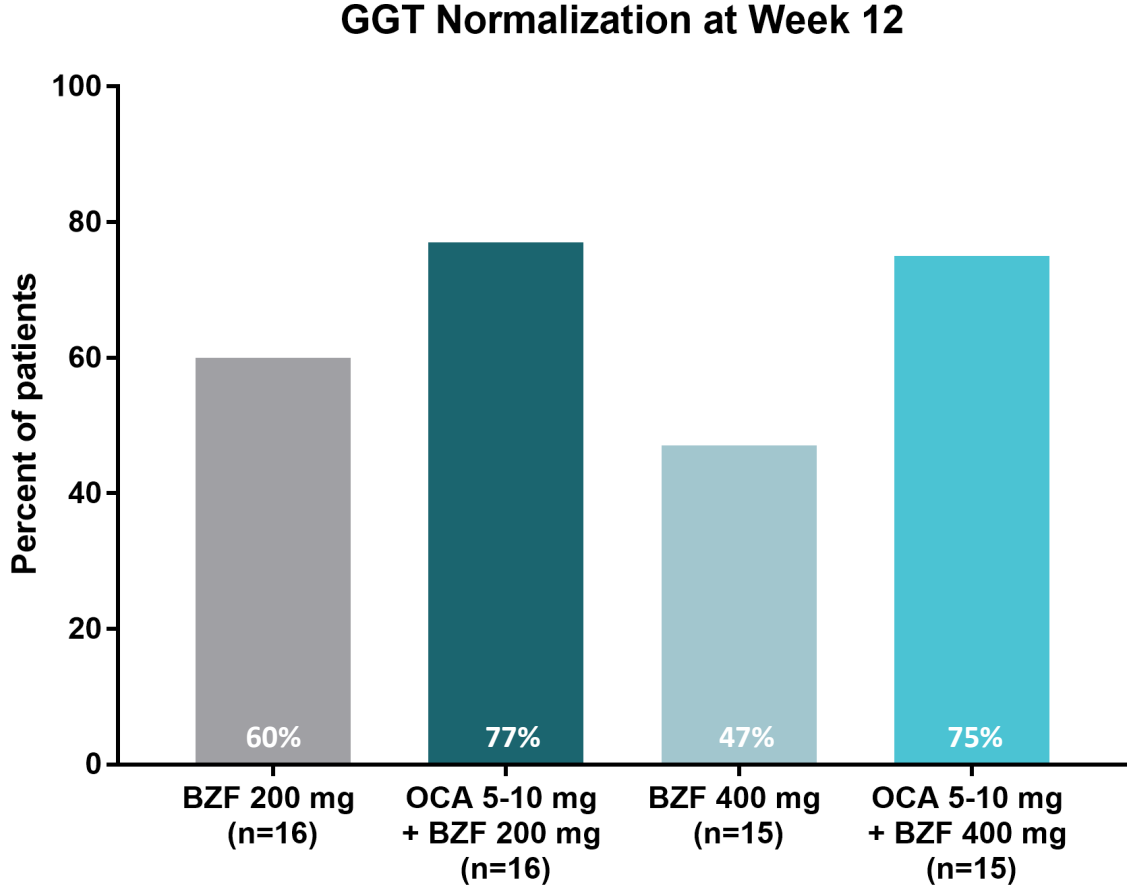




*Compared to BZF active-comparator; #Paired t-test compared to baseline at week 12 $p<0.001$.
Data are shown as LS mean values ± standard error of the mean.
Abbreviations: ALP, alkaline phosphatase; BZF, bezafibrate; LS, least-squares; OCA, obeticholic acid.

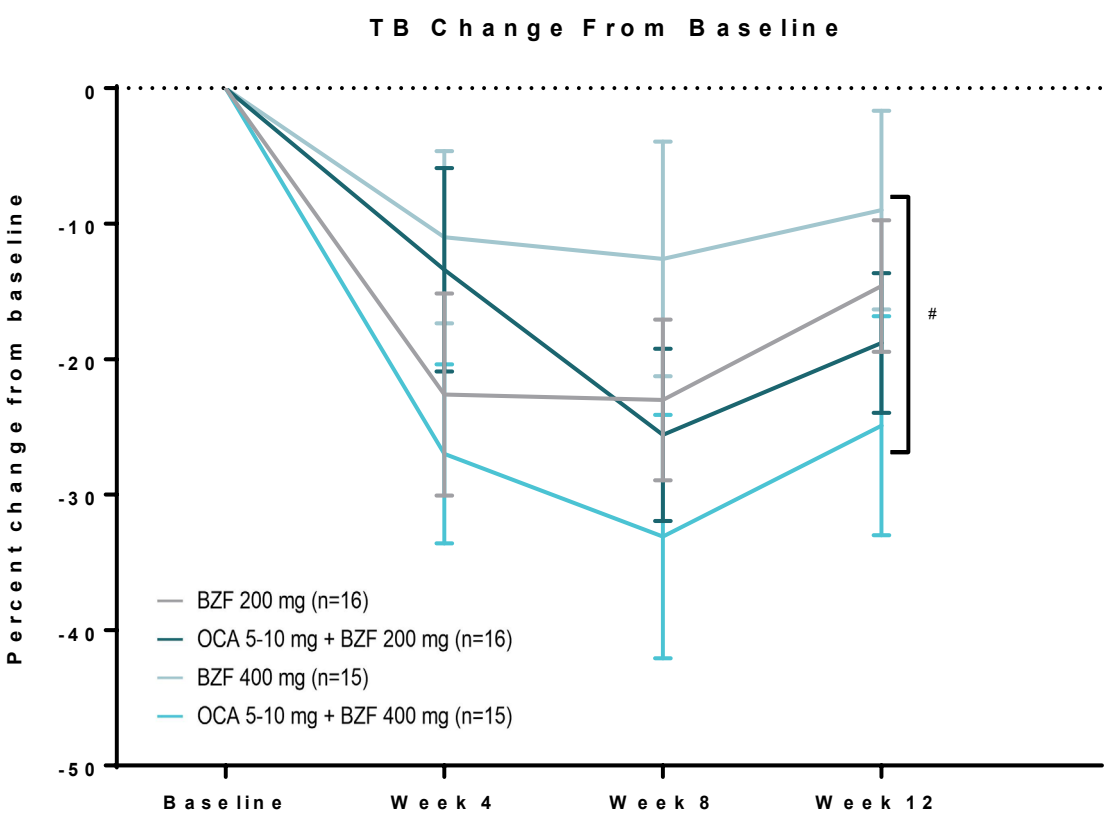
Both Combination Arms Induced a Rapid and Greater Normalization of GGT Relative to BZF Through Week 12

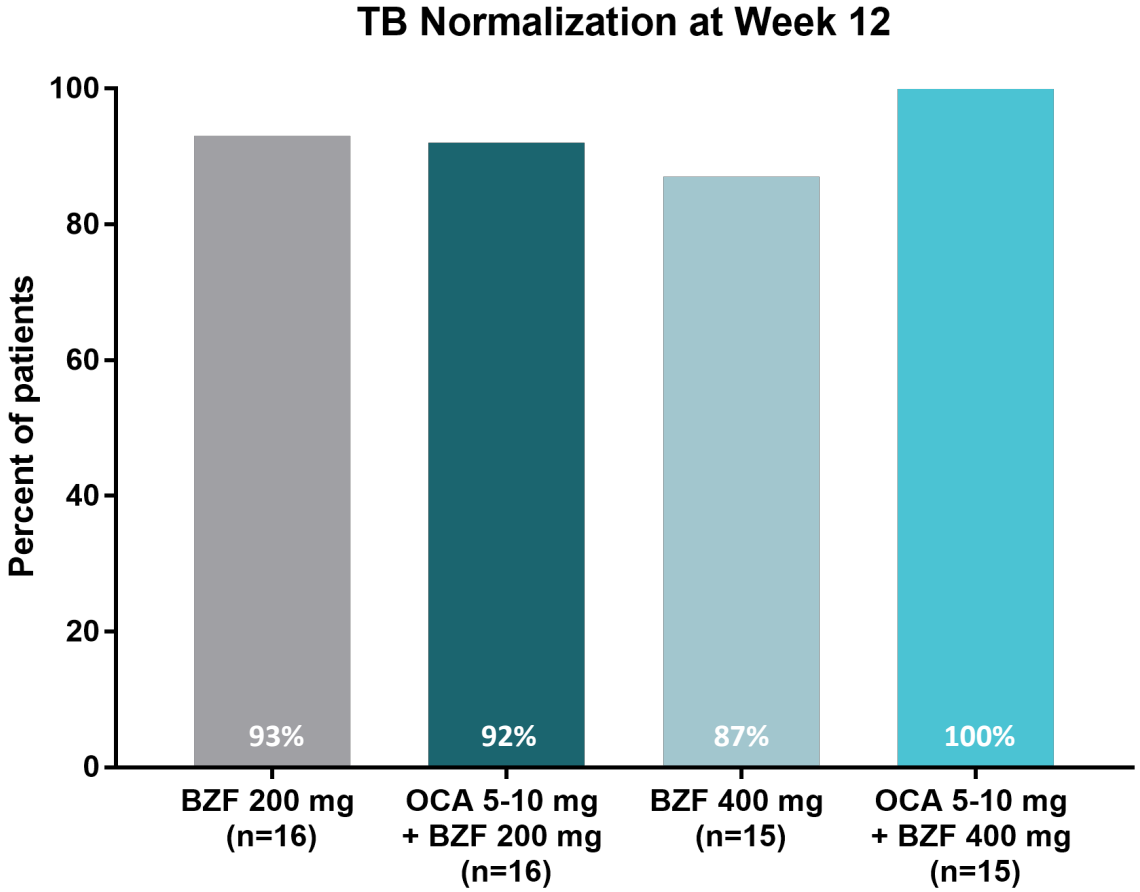




*Compared to BZF active-comparator; #Paired t-test compared to baseline at week 12 $p<0.01$.
Data are shown as LS mean values ± standard error of the mean.
Abbreviations: BZF, bezafibrate; GGT, gamma-glutamyl transferase; LS, least-squares; OCA, obeticholic acid.

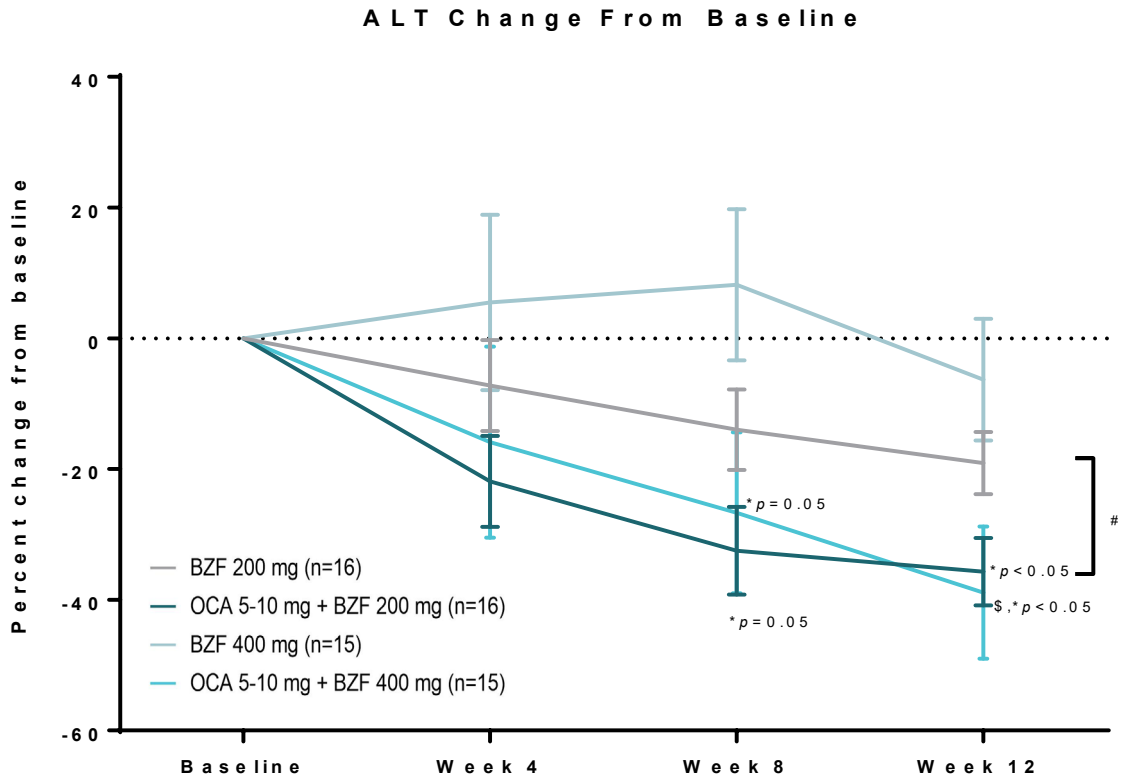
OCA 5-10 mg + BZF 400 mg had the Greatest Change From Baseline in Total Bilirubin and 100% Reduction to ≤0.6x ULN at Week 12

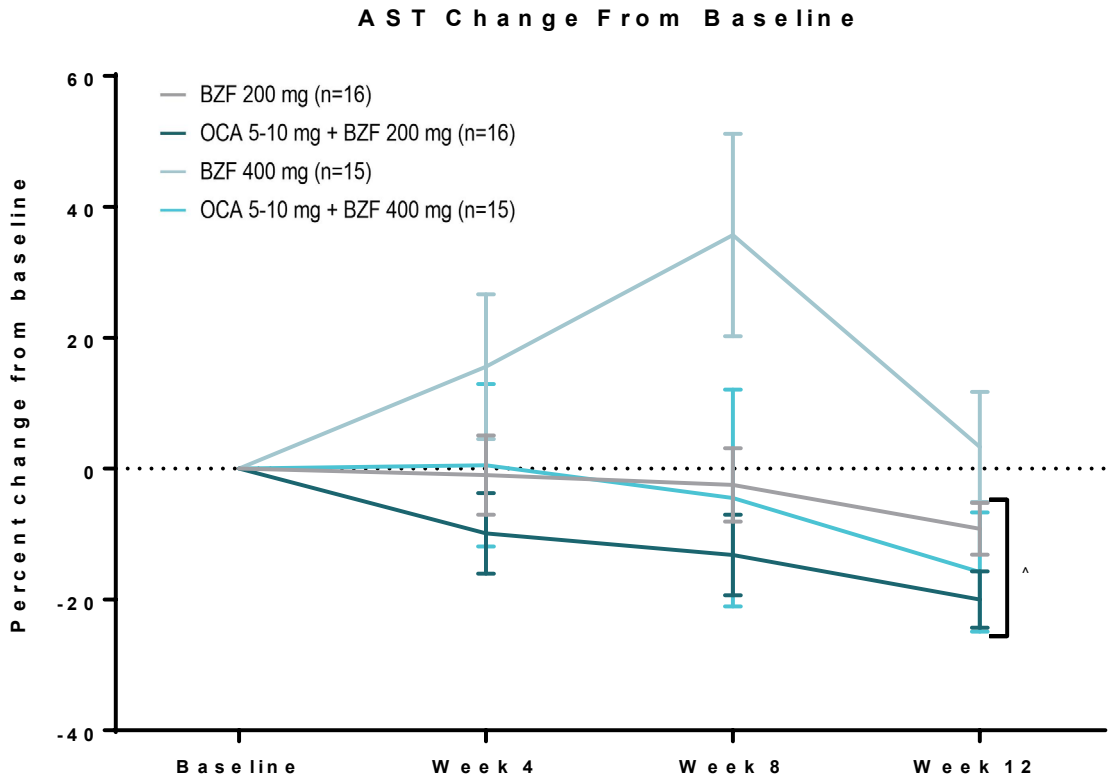




#Paired t-test compared to baseline at week 12 $p<0.01$.
Data are shown as LS mean values ± standard error of the mean.
Abbreviations: BZF, bezafibrate; LS, least-squares; OCA, obeticholic acid; TB, total bilirubin; ULN, upper limit of normal.

Both Combination Arms Induced a Rapid and Greater Normalization of ALT and AST Relative to BZF Through Week 12





ALT Normalization Rate for:
- OCA 5-10 mg + BZF 200 mg = 92%
- OCA 5-10 mg + BZF 400 mg = 100%

AST Normalization Rate for:
- OCA 5-10 mg + BZF 200 mg = 85%
- OCA 5-10 mg + BZF 400 mg = 92%

*Compared to BZF active-comparator; $Paired t-test compared to baseline at week 12 p <0.001; #Paired t-test compared to baseline at week 12 p<0.01;
^Paired t-test compared to baseline at week 12 p<0.05.
Data are shown as LS mean values ± standard error of the mean.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BZF, bezafibrate; LS, least-squares; OCA, obeticholic acid.

Summary of Adverse Events Through Week 12

All groups have comparable adverse event rates

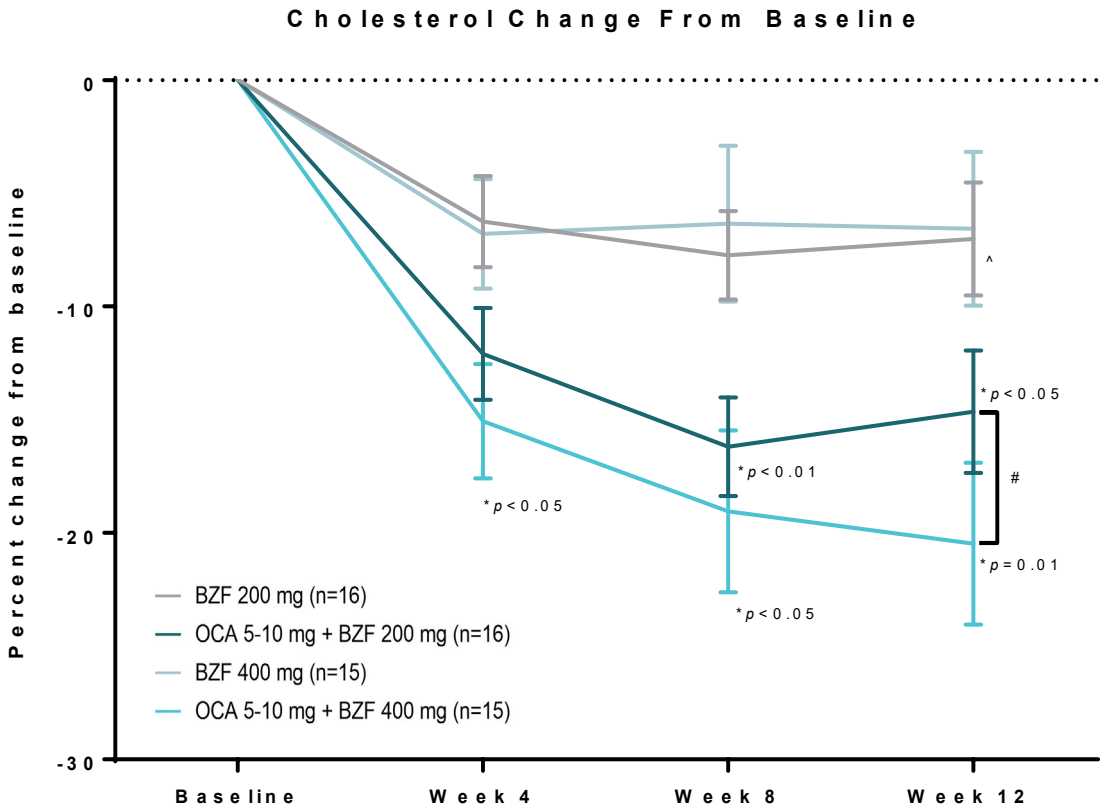
	BZF 200 mg (n=16) N (%)	OCA 5-10 mg + BZF 200 mg (n=16) N (%)	BZF 400 mg (n=15) N (%)	OCA 5-10 mg + BZF 400 mg (n=15) N (%)
Subjects with TEAE	**8** (50.0)	**11** (68.8)	**12** (80.0)	**9** (60.0)
Pruritus	**4** (25.0)	**4** (25.0)	**3** (20.0)	**2** (13.3)
Serious TEAEs	0	0	0	**1** (6.7)[a]
TEAE leading to discontinuation	0	0	0	**1** (6.7)[a]
TEAEs leading to death	0	0	0	0

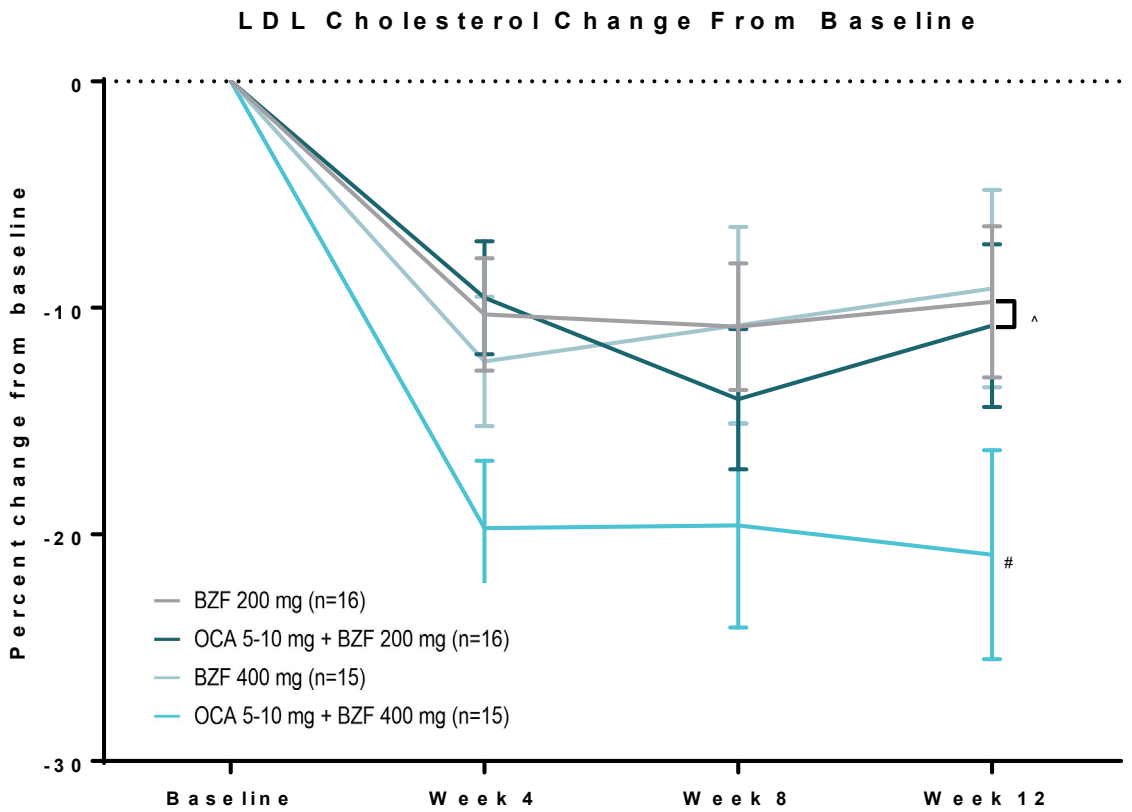
- Pruritus event rate in the combination groups of OCA 5-10 mg + BZF was 19.4%
- No difference in Gastrointestinal or Musculoskeletal adverse events between groups

[a]1 event of pruritus led to discontinuation from the study.

Abbreviations: BZF, bezafibrate; OCA, obeticholic acid; TEAEs, treatment-emergent adverse events.

OCA 5-10 mg + BZF 400 mg Induced a Rapid and Greater Change in Cholesterol and LDL Cholesterol Relative to BZF Through Week 12





*Compared to BZF active-comparator; #Paired t-test compared to baseline at week 12 $p<0.001$; ^Paired t-test compared to baseline at week 12 $p<0.05$.
Data are shown as LS mean values ± standard error of the mean.
Abbreviations: BZF, bezafibrate; LS, least-squares; OCA, obeticholic acid.

Interim Conclusions

- Combination OCA 5-10 mg + BZF 400 mg:
  - Normalized all five cholestatic surrogate markers in 58% of patients, suggesting biochemical remission of the cholestatic liver
  - Normalized ALP in 75% of patients, compared to 40% in the active comparator, BZF 400 mg
  - Induced a greater change in ALP from baseline (-63%), compared to the active comparator, BZF 400 mg (-40%)
  - Induced a rapid change in biomarkers, occurring as soon as week 4
- Low rates of pruritus were observed in the OCA 5-10 mg + BZF combination groups (mean 19.4%), which were lower than those described in the POISE study (placebo [38%], OCA 5-10 mg [56%], OCA 10 mg [68%])[1]
- The combination of OCA and BZF was well tolerated with low rates of adverse events

1. Nevens F, et al. *N Engl J Med*. 2016.
Abbreviations: ALP, alkaline phosphatase; BZF, bezafibrate; OCA, obeticholic acid.

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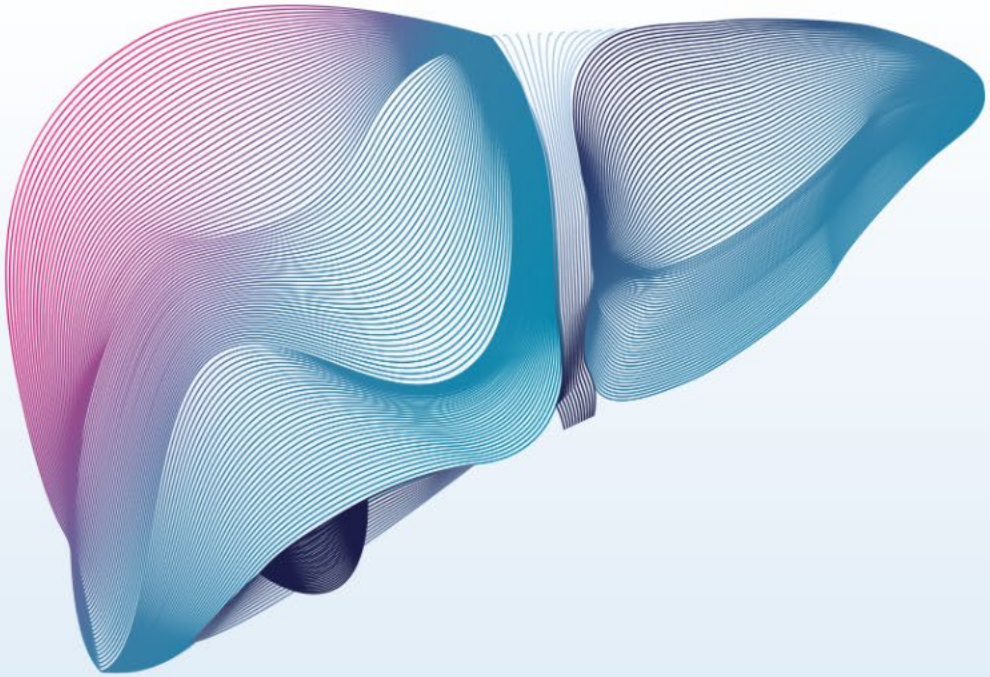

We would like to thank the patients who participated in these studies and the dedicated investigators who made this research possible.