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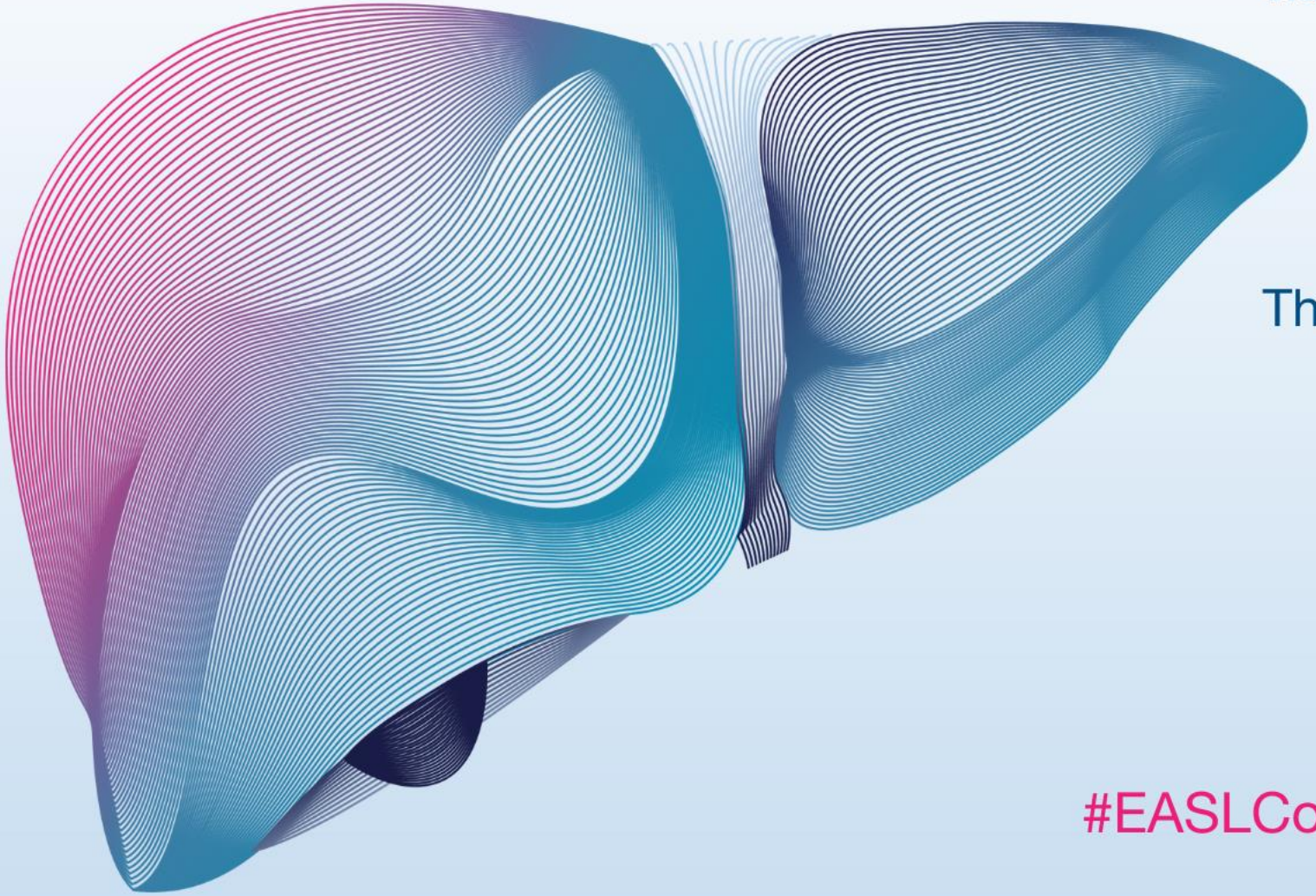

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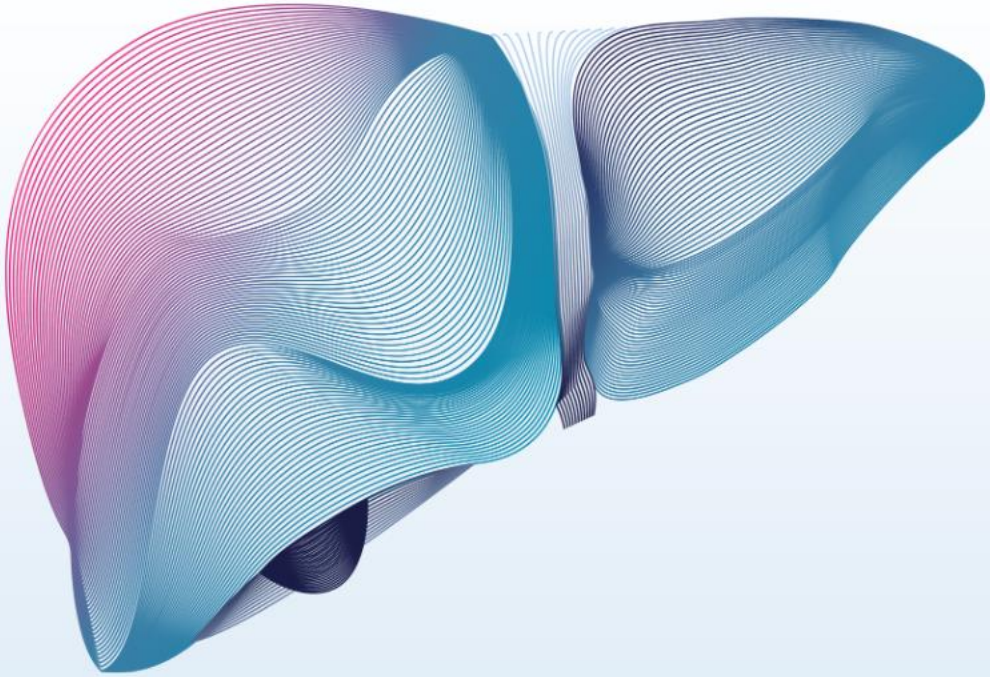

A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of cilofexor in patients with non-cirrhotic primary sclerosing cholangitis (PRIMIS)

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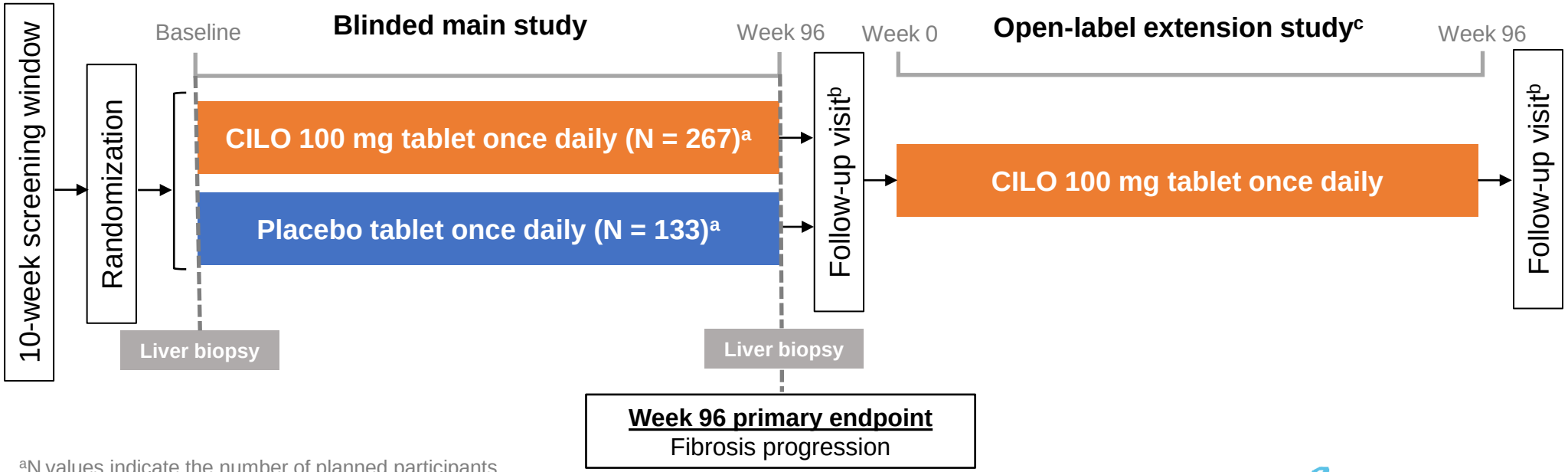
Background

- **Primary sclerosing cholangitis (PSC)** is a chronic progressive cholestatic liver disease with a poorly understood pathogenesis
- There are no approved therapies that can improve clinical outcomes in patients with PSC
- **Cilofexor** (CILO) is a selective, nonsteroidal farnesoid X receptor agonist
- A phase 2 trial in patients with non-cirrhotic PSC showed that treatment with CILO led to significant improvements in liver biochemistries and markers of cholestasis, and was well tolerated[1]
- **PRIMIS** was a phase 3, double-blind, randomized, placebo-controlled, multi-center trial (NCT03890120) designed to assess the efficacy and safety of CILO for the treatment of non-cirrhotic PSC

1. Trauner M, et al. *Hepatology* 2019;70:788–801.

PRIMIS study design

- Adults (18–75 years) with large duct PSC and liver fibrosis F0–F3 (Batts–Ludwig stage) were randomized 2:1 to receive CILO 100 mg or placebo orally once daily for 96 weeks
- Patients were stratified by the presence or absence of ursodeoxycholic acid use and presence or absence of bridging fibrosis (Batts–Ludwig fibrosis stage F3 vs F0, F1 and F2)



[a]N values indicate the number of planned participants.
[b]Follow-up visit was 4 weeks after completion of the corresponding study phase.
[c]Patients who completed week 96 with an evaluable liver biopsy (stage F0–F3) were eligible to enter a 96-week open-label extension study.
CILO, cilofexor; PSC, primary sclerosing cholangitis.

Methods: eligibility criteria

Key inclusion criteria
• Adults 18–75 years of age
• Diagnosis of large duct PSC
• Evaluable liver biopsy at screening (central reading)
• Platelet count ≥ 150 000/mm^3
• INR ≤ 1.4
• ALT ≤ 8 x ULN
• Total bilirubin < 2 mg/dL
• eGFR ≥ 30 mL/min
• UDCA dose must have been stable for ≥ 6 months before screening or no UDCA use for ≥ 6 months before screening
• Biologic, immunosuppressant or systemic corticosteroid dose must have been stable for ≥ 3 months before screening and remain stable throughout the trial

Key exclusion criteria
• Current or previous history of:
○ cirrhosis
○ liver transplantation
○ cholangiocarcinoma or hepatocellular carcinoma
○ ascending cholangitis in the 30 days prior to screening
• Other causes of liver disease
• CP score > 6
• MELD score > 12
• Moderate to severe inflammatory bowel disease[a]

[a]Defined as having a partial Mayo score > 4 and/or a rectal bleeding domain > 1 (unless bleeding is due to perianal disease) at screening.
ALT, alanine transaminase; CP, Child–Pugh; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; MELD, model for end-stage liver disease; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Methods: trial endpoints and interim analysis

Efficacy assessments

- The **primary endpoint** was the proportion of patients with progression of liver fibrosis (defined as a ≥ 1-stage increase in fibrosis [Batts–Ludwig stage]) at week 96
- **Secondary endpoints** included:
  - proportion of patients with fibrosis improvement (Batts–Ludwig stage) at week 96
  - proportion of patients with ≥ 25% reduction in alkaline phosphatase (ALP) levels from baseline and an absence of fibrosis worsening (Batts–Ludwig stage) at week 96
  - change from baseline to week 96 in liver enzymes, bile acids, enhanced liver fibrosis (ELF) scores, liver stiffness by vibration-controlled transient elastography (FibroScan) and PSC symptoms

Safety assessments included adverse events, clinical laboratory tests and vital sign assessments

Interim futility analysis

- A pre-planned, interim futility analysis was performed after 160 participants had either completed week 96 or an early termination visit. Early trial termination was considered if the likelihood of meeting the primary endpoint was ≤ 10%, based on a predictive power approach

CILO, cilofexor; PSC, primary sclerosing cholangitis.

Results: Baseline characteristics

Baseline characteristic	CILO 100 mg (N = 277)	Placebo (N = 139)	Total (N = 416)
Age, years	42 (33–52)	45 (34–55)	43 (34–54)
Women	107 (38.6)	52 (37.4)	159 (38.2)
Body mass index, kg/m^2	24.6 (22.2–27.9)	25.3 (23.1–29.2)	24.9 (22.7–28.1)
Concomitant UCDA	166 (59.9)	80 (57.6)	246 (59.1)
IBD	195 (70.4)	97 (69.8)	292 (70.2)
ALP, U/L	173 (107–274)	183 (108–328)	173 (107–293)
ALP category > 1.5 x ULN	126 (45.5)	71 (51.1)	197 (47.4)
Fasting total bile acids, µmol/L	10.4 (4.9–25.2)	9.5 (4.9–24.4)	10.0 (4.9–24.9)
ALT, U/L	50 (27–93)	50 (26–94)	50 (26–94)
Total bilirubin, mg/dL	0.6 (0.5–0.9)	0.6 (0.5–0.8)	0.6 (0.5–0.9)
Ludwig fibrosis stage			
0	49 (17.7)	27 (19.4)	76 (18.3)
1	73 (26.4)	40 (28.8)	113 (27.2)
2	84 (30.3)	38 (27.3)	122 (29.3)
3	71 (25.6)	34 (24.5)	105 (25.2)
ELF test score	9.06 (8.42–9.79)	9.04 (8.41–9.65)	9.06 (8.41–9.71)
Liver stiffness by FibroScan, kPa	7.0 (5.2–9.2)	7.0 (5.5–9.4)	7.0 (5.3–9.2)
MELD score	6 (6, 7)	6 (6, 7)	6 (6, 7)

All data are median (IQR) or n (%).
ALP, alkaline phosphatase; CILO, cilofexor; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; IQR, interquartile range; MELD, model for end-stage liver disease; UCDA, ursodeoxycholic acid; ULN, upper limit of normal.

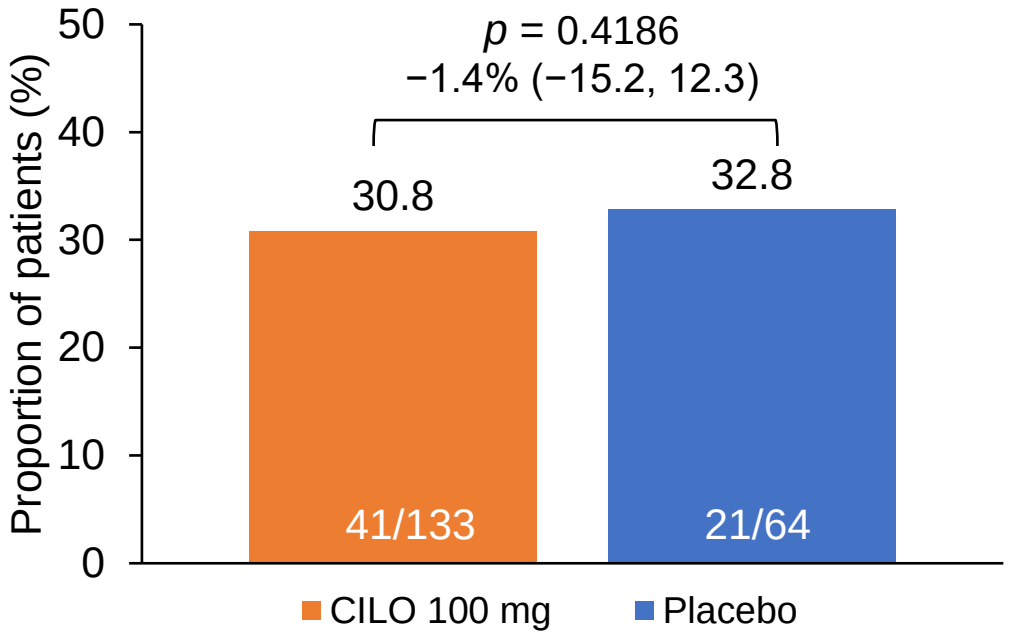
Results: patient disposition

Patient disposition, n (%)[a]	CILO 100 mg	Placebo	Total
Randomized	278	141	419
Randomized and treated	277	139	416
Completed trial drug	131 (47.3)	69 (49.6)	200 (48.1)
With protocol-specified clinical events[b]	6 (2.2)	5 (3.6)	11 (2.6)
Without protocol-specified clinical events	125 (45.1)	64 (46.0)	189 (45.4)
Prematurely discontinued trial drug	146 (52.7)	70 (50.4)	216 (51.9)
Study termination by sponsor	114 (41.2)	55 (39.6)	169 (40.6)
Adverse event	23 (8.3)	4 (2.9)	27 (6.5)
Withdrew consent	7 (2.5)	4 (2.9)	11 (2.6)
Investigator's discretion	1 (0.4)	3 (2.2)	4 (1.0)
Lost to follow up	1 (0.4)	1 (0.7)	2 (0.5)
Non-compliance with trial drug	0	2 (1.4)	2 (0.5)
Pregnancy	0	1 (0.7)	1 (0.2)

[a]Values are based on the number of randomized and treated patients.
[b]Patients who experienced protocol-specified clinical events (defined as histologic or clinical progression to cirrhosis, hepatic decompensation, liver transplantation or meeting minimal listing criteria for transplantation [i.e. MELD score ≥ 15], all-cause mortality, cholangiocarcinoma and hepatocellular carcinoma) were not considered to have discontinued treatment prematurely.
CILO, cilofexor; MELD, model for end-stage liver disease.

Results: patients with liver fibrosis progression at week 96

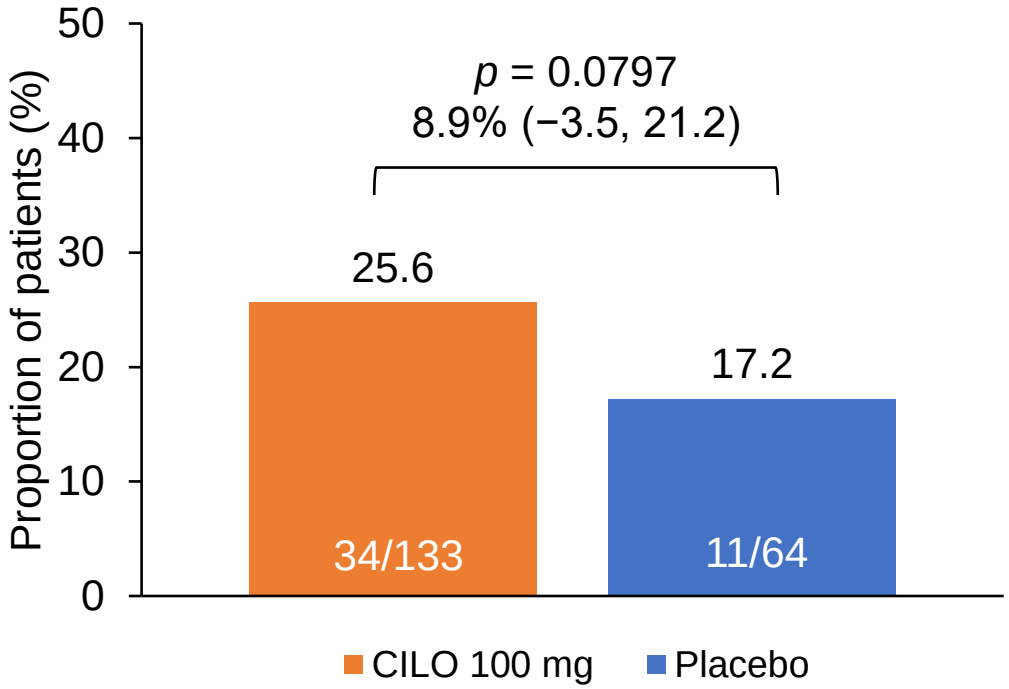
- The trial was terminated early because the interim futility analysis showed that the estimated probability of meeting the primary endpoint was 6.8%
- At week 96, the proportion of patients with a **≥ 1-stage increase in fibrosis** (Batts–Ludwig stage) was 30.8% in the CILO group compared with 32.8% in the placebo group



Treatment difference and associated 95% CI and one-sided *p* value were obtained by the stratum-adjusted Mantel–Haenszel method with baseline ursodeoxycholic acid use and Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as stratification factors.
CI, confidence interval; CILO, cilofexor.

Results: patients with liver fibrosis improvement at week 96

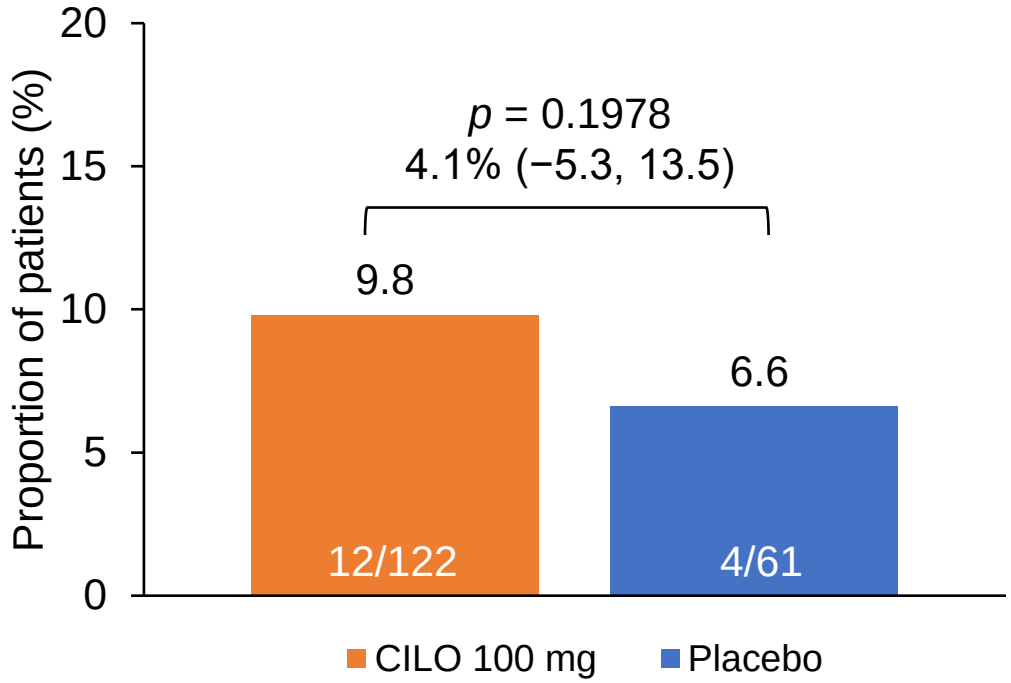
- At week 96, the proportion of patients with **fibrosis improvement** (≥ 1-stage decrease in Batts–Ludwig stage) was 25.6% in the CILO group compared with 17.2% in the placebo group



Treatment difference and associated 95% CI and one-sided nominal *p* value were obtained by the stratum-adjusted Mantel–Haenszel method with baseline ursodeoxycholic acid use and Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as stratification factors.
CI, confidence interval; CILO, cilofexor.

Results: patients with ≥ 25% reduction in ALP levels and an absence of fibrosis worsening at week 96

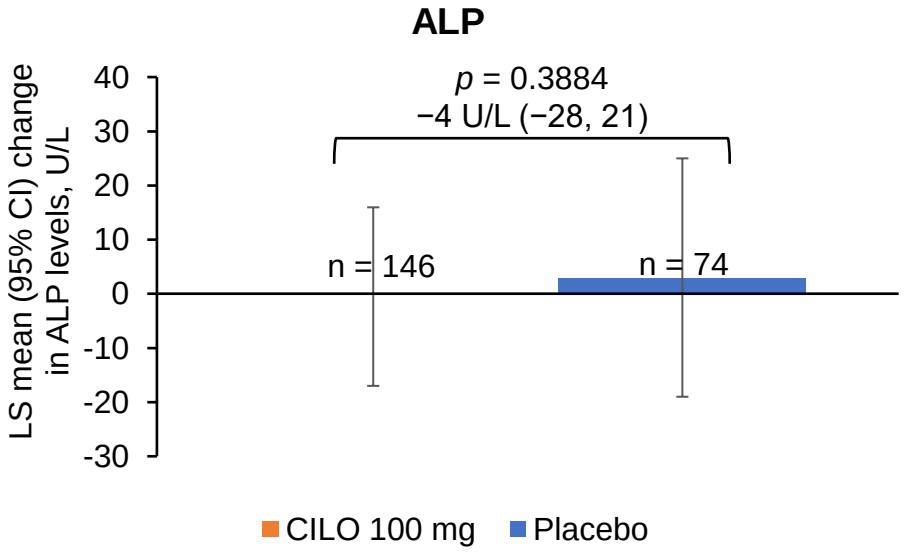
- At week 96, the proportion of patients with **≥ 25% reduction in ALP** levels from baseline **and** an **absence of fibrosis worsening** (Batts–Ludwig stage) was 9.8% in the CILO group compared with 6.6% in the placebo group

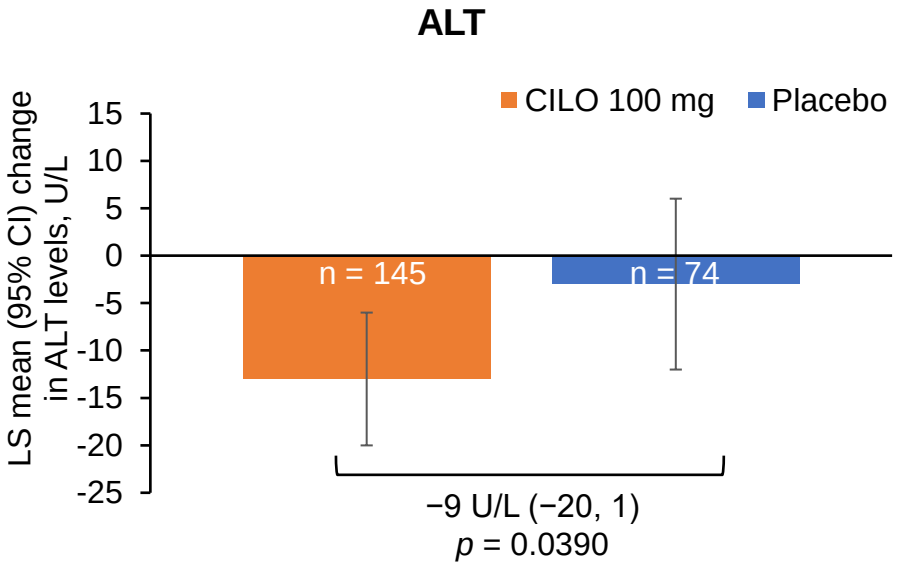


Treatment difference and associated 95% CI and one-sided nominal *p* value were obtained by the stratum-adjusted Mantel–Haenszel method with baseline ursodeoxycholic acid use and Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as stratification factors.
ALP, alkaline phosphatase; CI, confidence interval; CILO, cilofexor.

Results: change from baseline in liver enzymes

- Least-squares (LS) mean changes (95% CI) from baseline to week 96 were:
  - 0 U/L (−17, 16) for **ALP** levels in the CILO 100 mg group and +3 U/L (−19, 25) in the placebo group
  - −13 U/L (−20, −6) for **ALT** levels was in the CILO 100 mg group and −3 U/L (−12, 6) in the placebo group

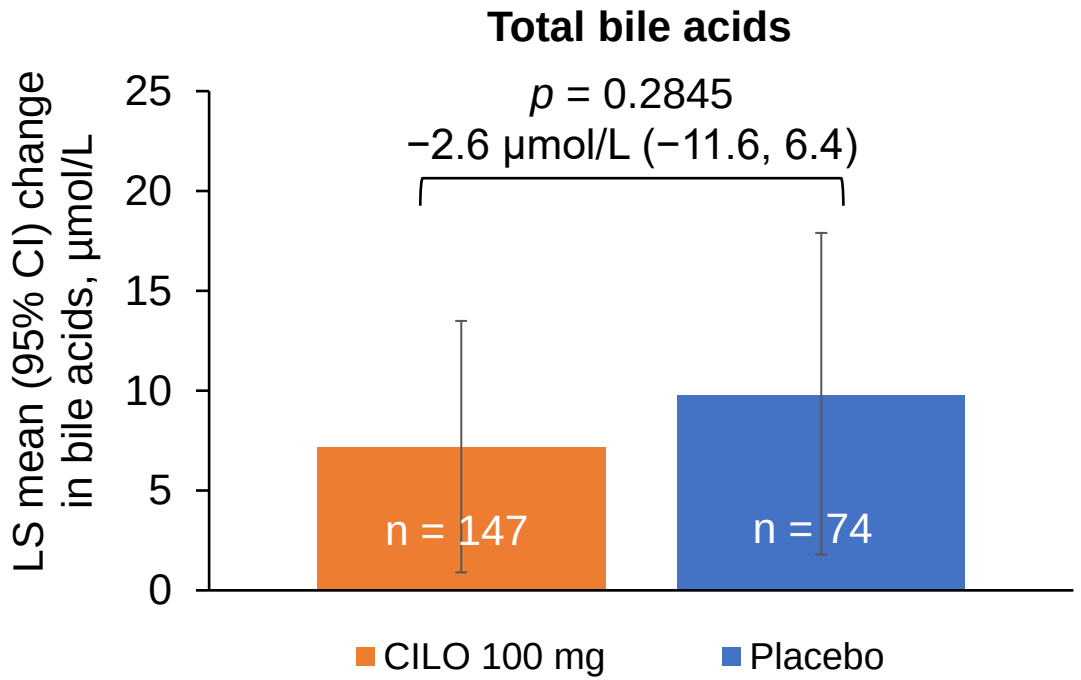




The LS means, 95% CIs, and one-sided nominal *p* values were obtained by an ANCOVA model with change from baseline at week 96 in the outcome measure as the dependent variable, and treatment group, baseline value of the outcome measure, baseline ursodeoxycholic acid use and baseline Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as independent variables.
ALP, alkaline phosphatase; ALT, alanine transaminase; ANCOVA, analysis of covariance; CI, confidence interval; CILO, cilofexor; LS, least-squares.

Results: change from baseline in fasting total bile acids

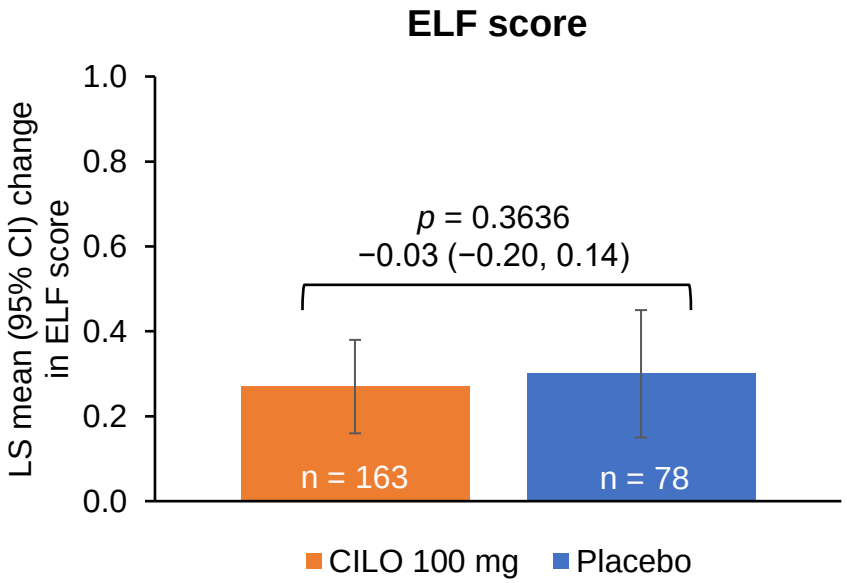
- The LS mean change (95% CI) from baseline to week 96 in **fasting total bile acids** was +7.2 µmol/L (0.9, 13.5) in the CILO 100 mg group and +9.8 µmol/L (1.8, 17.9) in the placebo group

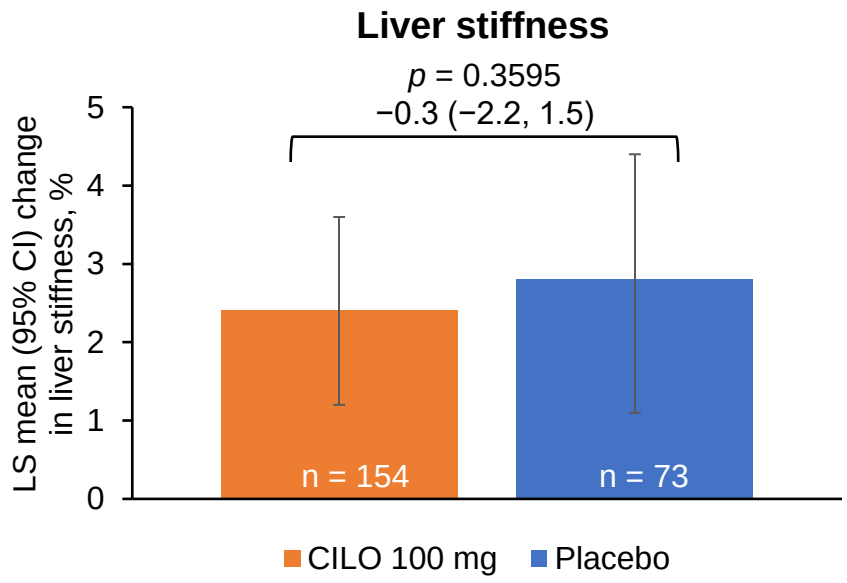


The LS means, 95% CIs, and one-sided nominal *p* values were obtained by an ANCOVA model with change from baseline at week 96 in the outcome measure as the dependent variable, and treatment group, baseline value of the outcome measure, baseline ursodeoxycholic acid use and baseline Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as independent variables.
ANCOVA, analysis of covariance; CI, confidence interval; CILO, cilofexor; LS, least-squares.

Results: change from baseline in markers of fibrosis

- LS mean changes (95% CIs) from baseline to week 96 were:
  - +0.27 (0.16, 0.38) for **ELF score** in the CILO 100 mg group and +0.30 (0.15, 0.45) in the placebo group
  - +2.4 kPa (1.2, 3.6) for **liver stiffness** (by FibroScan) in the CILO 100 mg group and +2.8 kPa (1.1, 4.4) in the placebo group

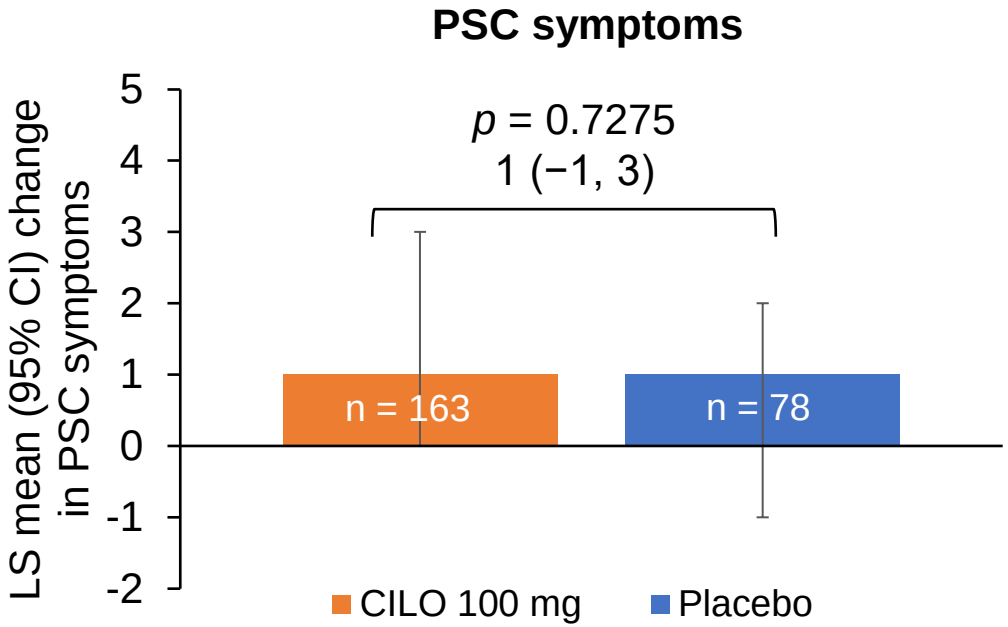




The LS means, 95% CIs, and one-sided nominal *p* values were obtained based on an ANCOVA model with change from baseline at week 96 in the outcome measure as the dependent variable, and treatment group, baseline value of the outcome measure, baseline ursodeoxycholic acid use and baseline Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as independent variables.
ANCOVA, analysis of covariance; CI, confidence interval; CILO, cilofexor; ELF, enhanced liver fibrosis; LS, least-squares.

Results: change from baseline in PSC symptoms

- The LS mean change (95% CI) from baseline to week 96 in **health-related quality of life** (based on disease-specific PSC patient-reported outcomes module 1) was +1 (0, 3) in the CILO 100 mg group and +1 (−1, 2) in the placebo group



The LS means, 95% CIs, and one-sided nominal *p* values were obtained based on an ANCOVA model with change from baseline at week 96 in the outcome measure as the dependent variable, and treatment group, baseline value of the outcome measure, baseline ursodeoxycholic acid use and baseline Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as independent variables.
ANCOVA, analysis of covariance; CI, confidence interval; CILO, cilofexor; LS, least-squares; PSC, primary sclerosing cholangitis.

Results: safety

TEAEs, n (%)	CILO 100 mg (N = 277)	Placebo (N = 139)
Any TEAE	269 (97.1)	132 (95.0)
Most common TEAE		
Pruritus	136 (49.1)	50 (36.0)
Pruritus (≥ grade 3)	11 (4.0)	1 (0.7)
COVID-19	65 (23.5)	26 (18.7)
Upper abdominal pain	40 (14.4)	20 (14.4)
TEAE related to study drug	134 (48.4)	50 (36.0)
TEAE leading to discontinuation of study drug	29 (10.5)	9 (6.5)
Protocol-specified clinical events[a]	6 (2.2)	5 (3.6)
All other TEAEs[b]	23 (8.3)	4 (2.9)
TE serious AE	53 (19.1)	26 (18.7)
TE serious AE related to study drug	9 (3.2)	5 (3.6)
Death	2 (0.7)	0
Grade 3–4 laboratory abnormality	22 (8.0)	14 (10.1)

[a]Patients with protocol-specified clinical events (defined as histologic or clinical progression to cirrhosis, hepatic decompensation, liver transplantation or meeting minimal listing criteria for transplantation [i.e. MELD score ≥ 15], all-cause mortality, cholangiocarcinoma and hepatocellular carcinoma) were not considered to have discontinued treatment prematurely.
[b]Patients with TEAEs that were not clinical events were considered to have been discontinued prematurely.
AE, adverse event; CILO, cilofexor; MELD, model for end-stage liver disease; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

Results: AEs leading to premature discontinuation of study drug

TEAEs leading to premature discontinuation of study drug, n (%)	CILO 100 mg (N = 277)	Placebo (N = 139)
Pruritus	8 (2.9)	0
Abdominal pain	3 (1.1)	0
Hyperbilirubinemia	2 (0.7)	0
Pyrexia	2 (0.7)	0
Blood bilirubin increased	1 (0.4)	0
Breast cancer metastatic	1 (0.4)	0
Child-Pugh-Turcotte score abnormal	1 (0.4)	0
Cholangitis	1 (0.4)	0
Diarrhoea	1 (0.4)	0
Diarrhoea haemorrhagic	1 (0.4)	0
Drug-induced liver injury	1 (0.4)	1 (0.7)
Fatigue	1 (0.4)	0
Feeling abnormal	1 (0.4)	0
Gastrointestinal pain	1 (0.4)	0
Headache	1 (0.4)	0
Hepatotoxicity	1 (0.4)	0
Hydrocholecystis	1 (0.4)	0
International normalised ratio increased	1 (0.4)	0
Jaundice	1 (0.4)	0
Liver abscess	1 (0.4)	0
Liver function test abnormal	1 (0.4)	0
Lung adenocarcinoma	1 (0.4)	0
Musculoskeletal chest pain	1 (0.4)	0
Alanine aminotransferase increased	0	1 (0.7)
Aspartate aminotransferase increased	0	1 (0.7)
Gastric cancer	0	1 (0.7)
Transaminases increased	0	1 (0.7)

CILO, cilofexor; TEAE, treatment-emergent adverse event.

Conclusions

- The PRIMIS study was terminated based on a pre-planned interim futility analysis that indicated a low probability (6.8%) of achieving its primary endpoint
- At week 96, the proportion of patients with a ≥ 1-stage increase in fibrosis was not significantly different between CILO (30.8%) and placebo (32.8%)
- At week 96, the proportions of patients with fibrosis improvement, and ≥ 25% reduction in ALP levels and an absence of fibrosis worsening were not significantly different between CILO and placebo
- Except for ALT levels, there were no notable changes from baseline to week 96 in markers of liver injury or fibrosis, or PSC symptoms with CILO versus placebo
- CILO was generally well tolerated in patients with non-cirrhotic PSC and was associated with an acceptable safety profile

ALP, alkaline phosphatase; ALT, alanine transaminase; CILO, cilofexor; PSC, primary sclerosing cholangitis.

Acknowledgements

- We thank the patients, their families and the study investigators who participated in this study.
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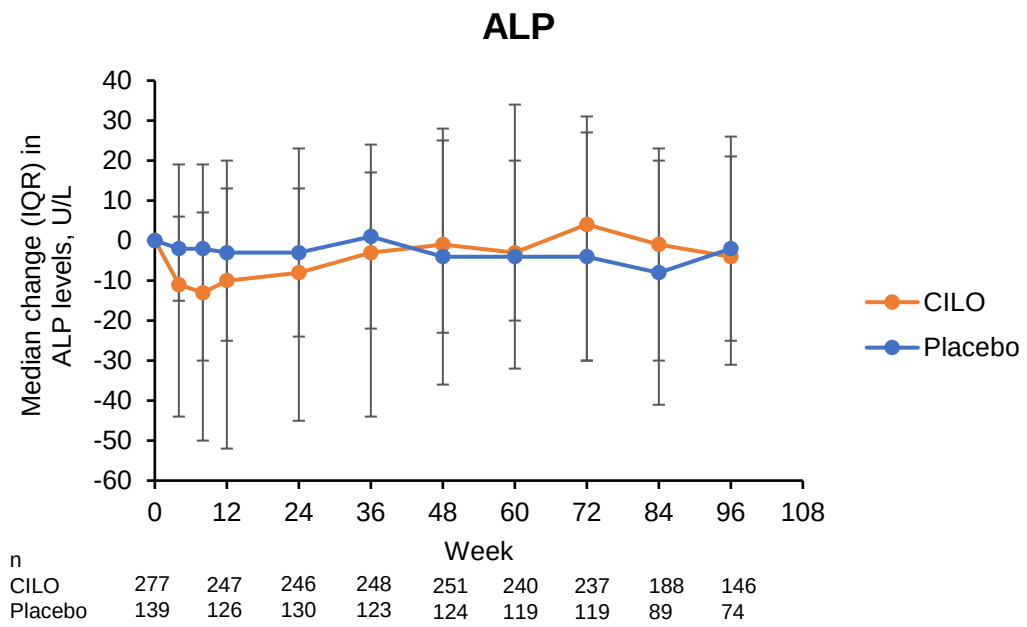
- Medical writing support was provided by Tamsyn Stanborough PhD of Oxford PharmaGenesis, Melbourne, Australia, in accordance with Good Publication Practice (GPP 2022) guidelines, and was funded by Gilead Sciences, Inc., Foster City, CA, USA

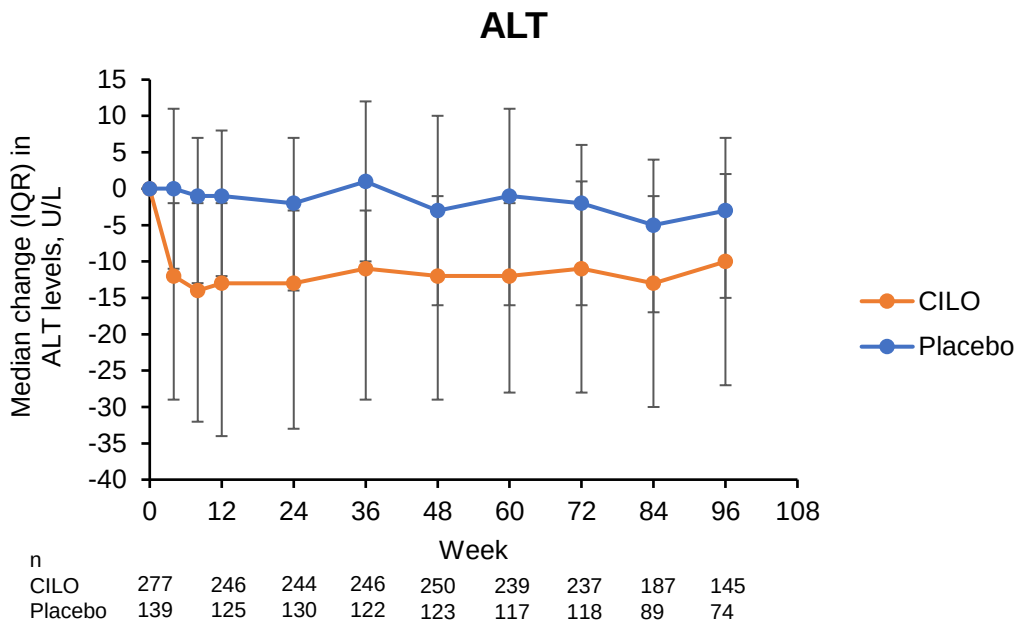
Additional slides

Results: changes from baseline in ALT levels over time

- Median (IQR) changes from baseline to week 96 in:
  - **ALP** levels were −4 U/L (−31, 26) in the CILO 100 mg group and −2 U/L (−25, 21) in the placebo group
  - **ALT** levels were −10 U/L (−27, 2) in the CILO 100 mg group and −3 U/L (−15, 7) in the placebo group



n									
CILO	277	247	246	248	251	240	237	188	146
Placebo	139	126	130	123	124	119	119	89	74

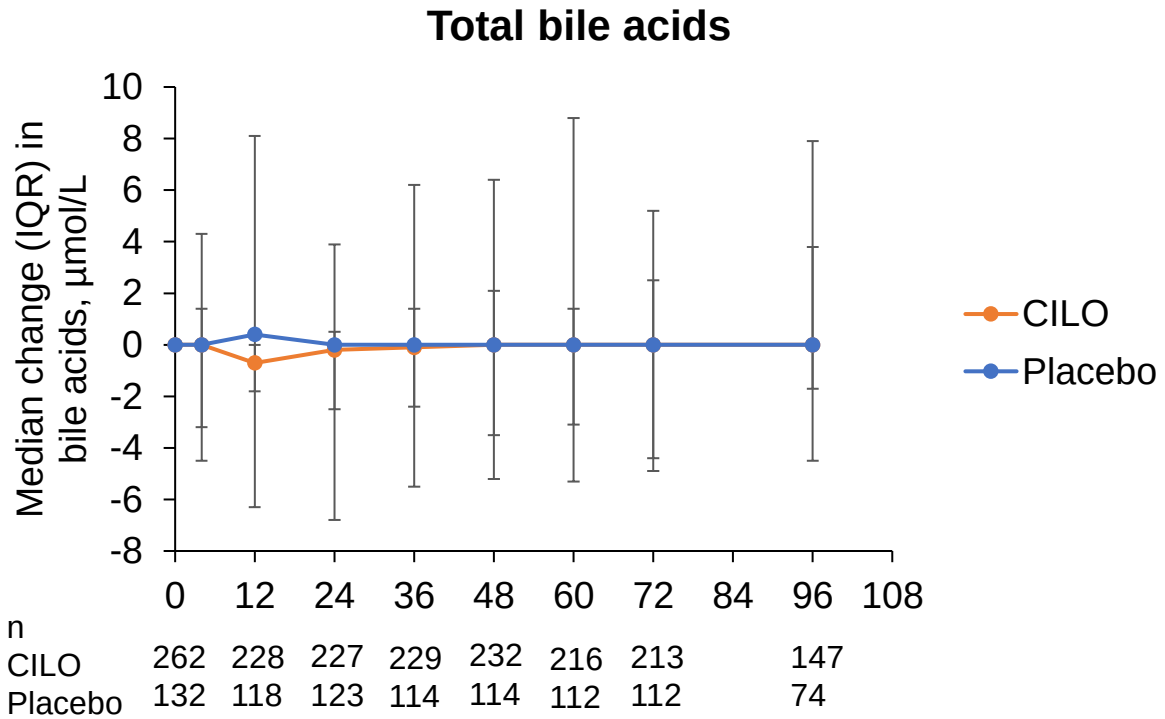


n									
CILO	277	246	244	246	250	239	237	187	145
Placebo	139	125	130	122	123	117	118	89	74

ALP, alkaline phosphatase; ALT, alanine transaminase; CILO, cilofexor; IQR, interquartile range.

Results: change from baseline in fasting total bile acids

- Median (IQR) changes from baseline to week 96 in **fasting total bile acids** were 0.0 (−4.5, 3.8) µmol/L in the CILO 100 mg group and 0.0 (−1.7, 7.9) µmol/L in the placebo group



CILO, cilofexor; IQR, interquartile range.

Results: protocol-specified clinical events leading to discontinuation of study drug

Protocol-specified clinical events leading to discontinuation of study drug, n (%)	CILO 100 mg (N = 277)	Placebo (N = 139)
Cholangiocarcinoma	1	4
Hepatic cirrhosis	3	0
Varices oesophageal	0	1
Qualification for liver transplant (MELD score ≥ 15)	1	0
Liver transplant	1	0

CILO, cilofexor; MELD, model for end-stage liver disease.