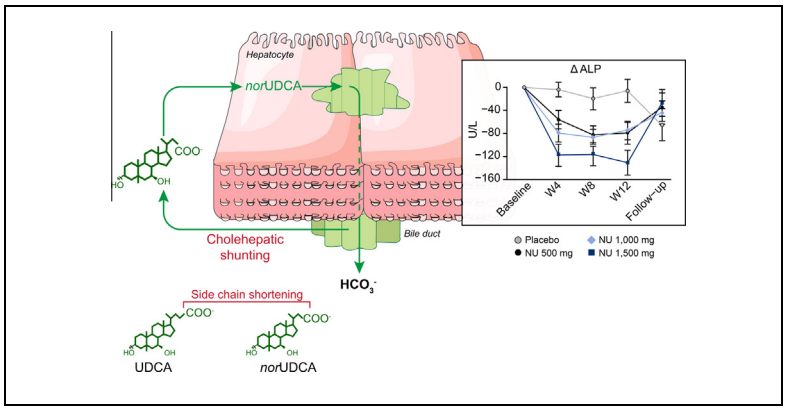
Research Article

JOURNAL OF HEPATOLOGY

# *nor*Ursodeoxycholic acid improves cholestasis in primary sclerosing cholangitis

## Graphical abstract




## Highlights

- There is an urgent need for novel drugs for PSC.
- In this phase II clinical trial, *nor*UDCA reduced serum ALP levels within 12 weeks.
- *nor*UDCA's effects on liver enzymes were dose-dependent.
- The safety profile of *nor*UDCA was excellent.

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## Lay summary

Effective medical therapy for primary sclerosing cholangitis (PSC) is urgently needed. In this phase II clinical study in PSC patients, a side chain-shortened derivative of ursodeoxycholic acid, *nor*ursodeoxycholic acid (*nor*UDCA), significantly reduced serum alkaline phosphatase levels in a dose-dependent manner during a 12-week treatment. Importantly, *nor*UDCA showed a favorable safety profile, which was similar to placebo. The use of *nor*UDCA in PSC patients is promising and will be further evaluated in a phase III clinical study.

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# *nor*Ursodeoxycholic acid improves cholestasis in primary sclerosing cholangitis

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See Editorial, pages 446–447

**Background & Aim**: Primary sclerosing cholangitis (PSC) represents a devastating bile duct disease, currently lacking effective medical therapy. 24-*nor*ursodeoxycholic acid (*nor*UDCA) is a side chain-shortened $C_{23}$ homologue of UDCA and has shown potent anti-cholestatic, anti-inflammatory and anti-fibrotic properties in a preclinical PSC mouse model. A randomized controlled trial, including 38 centers from 12 European countries, evaluated the safety and efficacy of three doses of oral *nor*UDCA (500 mg/d, 1,000 mg/d or 1,500 mg/d) compared with placebo in patients with PSC.

**Methods**: One hundred sixty-one PSC patients without concomitant UDCA therapy and with elevated serum alkaline phosphatase (ALP) levels were randomized for a 12-week treatment followed by a 4-week follow-up. The primary efficacy endpoint was the mean relative change in ALP levels between baseline and end of treatment visit.

**Results**: *nor*UDCA reduced ALP levels by −12.3%, −17.3%, and −26.0% in the 500, 1,000, and 1,500 mg/d groups ($p = 0.029$, $p = 0.003$, and $p < 0.0001$ when compared to placebo), respectively, while a +1.2% increase was observed in the placebo group. Similar dose-dependent results were found for secondary endpoints, such as ALT, AST, γ-GT, or the rate of patients achieving ALP levels $<1.5\times$ ULN. Serious adverse events occurred in seven patients in the 500 mg/d, five patients in the 1,000 mg/d, two patients in the 1500 mg/d group, and three in the placebo group. There was no difference in reported pruritus between treatment and placebo groups.

**Conclusions**: *nor*UDCA significantly reduced ALP values dose-dependently in all treatment arms. The safety profile of *nor*UDCA was excellent and comparable to placebo. Consequently, these results justify a phase III trial of *nor*UDCA in PSC patients.

**Lay summary:** Effective medical therapy for primary sclerosing cholangitis (PSC) is urgently needed. In this phase II clinical study in PSC patients, a side chain-shortened derivative of ursodeoxycholic acid, *nor*ursodeoxycholic acid (*nor*UDCA), significantly reduced serum alkaline phosphatase levels in a dose-dependent manner during a 12-week treatment. Importantly, *nor*UDCA showed a favorable safety profile, which was similar to placebo. The use of *nor*UDCA in PSC patients is promising and will be further evaluated in a phase III clinical study.

ClinicalTrials.gov number: NCT01755507.



Keywords: Alkaline phosphatase; Bile acid treatment; Cholestasis; Sclerosing cholangitis; Side chain-shortened bile acids; Cholehepatic shunting; Ursodeoxycholic acid.

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