were defined as patients who did not.

The researchers found that 95 responders (48%) and 101 incomplete responders (52%) had ALP of less than 1.67 times the ULN, 179 responders (91%) and 18 incomplete responders (9%) had total bilirubin of less than or equal to the ULN, and 131 responders (67%) and 65 incomplete responders (33%) experienced a decrease in ALP of at least 15%.

The researchers analyzed changes from baseline in ALP, ALT, AST, GGT, and bilirubin (total and direct) for responders and incomplete responders. Figure 3 shows the mean change from baseline in ALP for responders and incomplete responders. The mean change from baseline at year 5 for responders and incomplete responders was –19 U/L and –28 U/L, respectively, for ALT; –9 U/L and –16 U/L, respectively, for AST; and 155 U/L and 165 U/L, respectively, for GGT. In addition, responders and incomplete responders experienced similar mean changes from baseline in direct bilirubin over the 72 months of the extension study. Pruritus was the most common adverse event among both responders and incomplete responders, but caused few patients to discontinue treatment.

The researchers concluded that OCA improved important biochemical markers of PBC, regardless of meeting the POISE primary endpoint, following 1 year of treatment with OCA. Changes in biochemical markers over time were frequently similar between groups, suggesting that the POISE primary endpoint does not completely capture the benefit of OCA.

References

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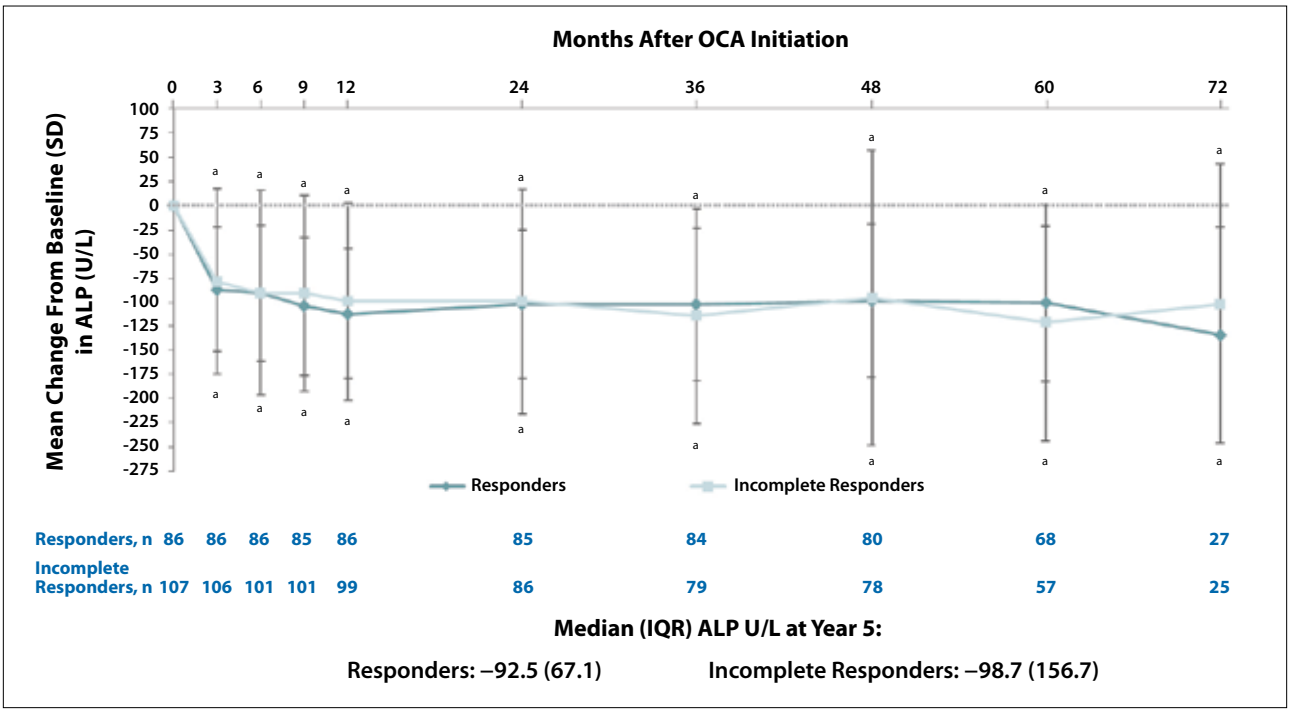

Figure 3. Mean (SD) change from baseline in ALP levels through month 72 by responder subgroup. [a]*P*<.05 vs baseline. ALP, alkaline phosphatase; IQR, interquartile range; OCA, obeticholic acid; SD, standard deviation. Adapted from Hansen BE et al. AASLD abstract 1251. *Hepatology*. 2020;72(suppl 1).[2]

ENHANCE: Safety and Efficacy of Seladelpar in Patients With Primary Biliary Cholangitis—A Phase 3, International, Randomized, Placebo-Controlled Study

Seladelpar is currently under investigation as a second-line treatment for PBC.[1] It is a potent and selective peroxisome proliferator-activated receptor (PPAR)-delta agonist, targeting a receptor found in hepatocytes, cholangiocytes, Kupffer cells, macrophages, and stellate cells—cell types that play a key role in liver disease. PPAR-delta agonism with seladelpar is both anti-inflammatory and antifibrotic. This approach also

reduces bile acids and increases lipid metabolism.

The phase 3 ENHANCE study investigated the use of seladelpar in patients with PBC who did not respond to first-line treatment, and findings were presented by Dr Gideon M. Hirschfield at the AASLD 2020 Liver Meeting Digital Experience.[2] Patients diagnosed with PBC were randomized to 1 of 3 treatment arms: seladelpar 10 mg (80 patients), seladelpar 5 mg for 26 weeks followed by an additional 26 weeks of either 5 mg or 10 mg (80 patients), or placebo (80 patients). The primary endpoint was a composite response by month 3 that included ALP of less than 1.67 times the ULN, a 15% or greater decrease in ALP, and total bilirubin at or below the ULN. The researchers also looked at whether ALP was normalized by month 3 and at the change from baseline in pruritus at month 3, and evaluated all of these measures at month 6.

An unexpected histologic finding in a clinical trial of seladelpar for nonalcoholic steatohepatitis led to early termination of the ENHANCE study. The finding turned out to be unrelated to the drug, but rather due to preexisting circumstance. The investigators conducted a blinded analysis following termination, as well as a safety analysis that included all patients who received at least 1 dose of seladelpar.

ABSTRACT SUMMARY Durability of Treatment Response After 1 Year of Therapy With Seladelpar in Patients With Primary Biliary Cholangitis: Final Results of an International Phase 2 Study

In this phase 2, open-label, uncontrolled, dose-finding study, 112 patients with PBC with an inadequate response to UDCA received seladelpar at a dose of 2 mg (11 patients), 5 mg (49 patients), or 10 mg (52 patients), with doses potentially increased up to 10 mg after 12 weeks, depending on biochemical response for 1 year (EASL abstract FRI133). Patients were mostly female and had an average age of 58 years. After a year of treatment, the mean decrease in ALP in the 5/10-mg group was 40%, and 45% in the 10-mg group. In the 5-mg group that escalated to 10 mg, 53% met the composite endpoint, as did 69% of patients who received 10 mg from the start.

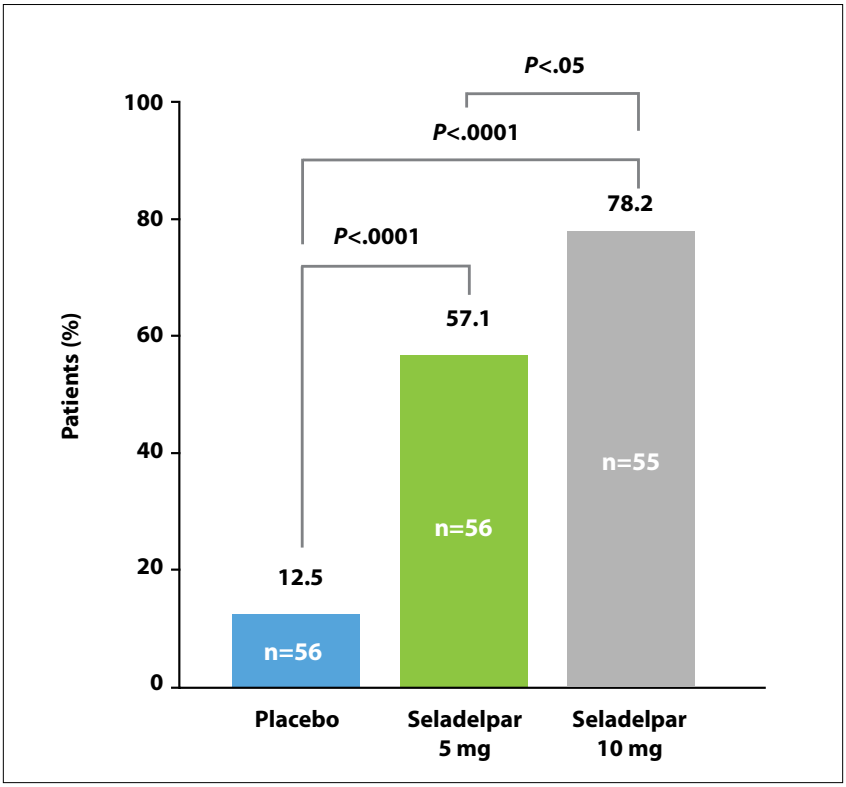

Figure 4. Primary composite endpoint achieved at 3 months with seladelpar. *P* values by Cochran-Mantel-Haenszel test. CymaBay, data on file 2020. Adapted from Hirschfield GM et al. AASLD abstract LO11. *Hepatology*. 2020;72(suppl 1).[2]

A composite response was achieved by 78.2% of patients in the 10-mg arm, 57.1% of patients in the 5-mg arm, and 12.5% of patients in the placebo arm (Figure 4). The response rates for the 5- and 10-mg arms were both statistically significantly higher than the rate for the placebo arm. The secondary endpoint of ALP normalization was achieved by 27.3% of patients in the 10-mg arm, 5.4% of patients in the 5-mg arm, and no patients in the placebo arm. The investigators reported an absolute reduction in ALP of nearly 45% with the 10-mg dose, a decrease of approximately 122 units. Other serum liver tests reflected a similar benefit from seladelpar.

Adverse events were mild to moderate. The most common issues were pruritus (13% in the placebo arm, 3% in the 5-mg arm, and 11% in the 10-mg arm) and abdominal pain (3%, 9%, and 7%, respectively). A 52-week phase 3 study of seladelpar is scheduled to begin in early 2021.

References

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