Comparative efficacy of elafibranor and seladelpar in patients with primary biliary cholangitis: A network meta-analysis

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KEY LEARNINGS:

Patients treated with elafibranor were significantly more likely to achieve cholestasis response than patients treated with seladelpar, without significant differences in the likelihood of other outcomes, including pruritus and alkaline phosphatase normalisation.

BACKGROUND

- Patients with primary biliary cholangitis (PBC) experience a substantial clinical burden, with disease progression associated with numerous symptoms, comorbidities and life-threatening, liver-related complications, including cirrhosis and hepatocellular carcinoma.[1,2]
- Elafibranor and seladelpar are two emerging treatments for the second-line treatment of PBC which have demonstrated substantial efficacy in the Phase III studies ELATIVE and RESPONSE, respectively.[3,4] However, there are currently no randomised controlled trials comparing them.

OBJECTIVE

The objective of the network meta-analysis (NMA) was to assess the comparative efficacy and safety of elafibranor and seladelpar in adult patients with PBC.

METHODS

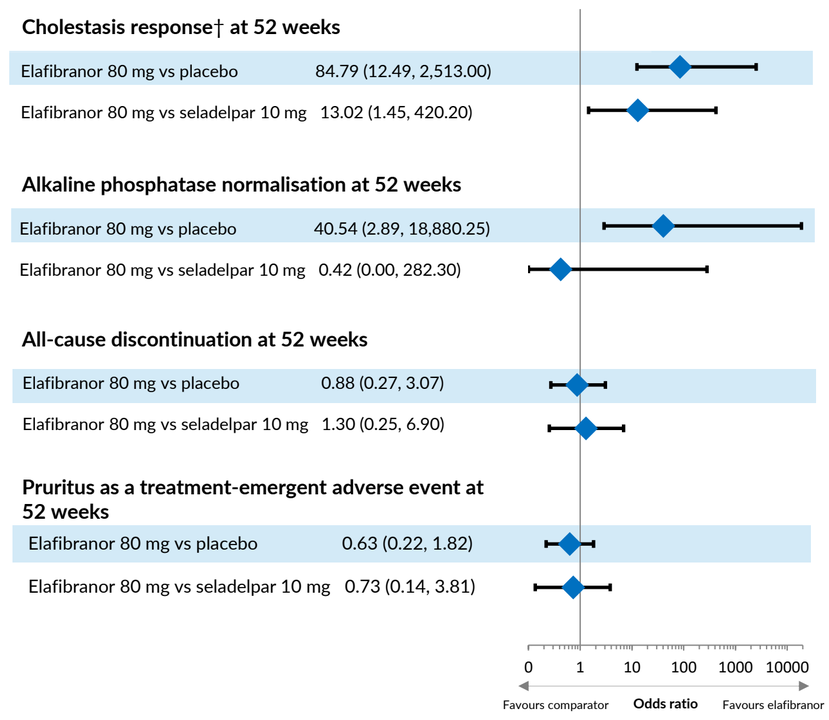
- Following a systematic literature review, a feasibility assessment of an indirect treatment comparison of elafibranor, seladelpar, and placebo using the ELATIVE and RESPONSE studies was performed.
  - Minimal heterogeneity was identified; study design and treatment effect modifiers were found to be comparable.
- Differences in the upper limit of normal definitions for alkaline phosphatase and total bilirubin in trial eligibility and outcomes were identified between ELATIVE and RESPONSE.
  - Upper limits of normal from RESPONSE were implemented in the ELATIVE individual patient data to exclude patients who would not be eligible for RESPONSE and re-calculate outcomes.
- With this, and in the absence of other heterogeneity, population adjustment was not needed, and a Bayesian NMA was performed.
- Following National Institute for Health and Care Excellence Decision Support Unit guidance[5], random effects NMAs were performed for the base case analysis. Binary and continuous outcomes after 52 weeks of treatment were estimated.
- Posterior probabilities were generated for the likelihood of elafibranor having more favourable outcomes than seladelpar or placebo.

RESULTS

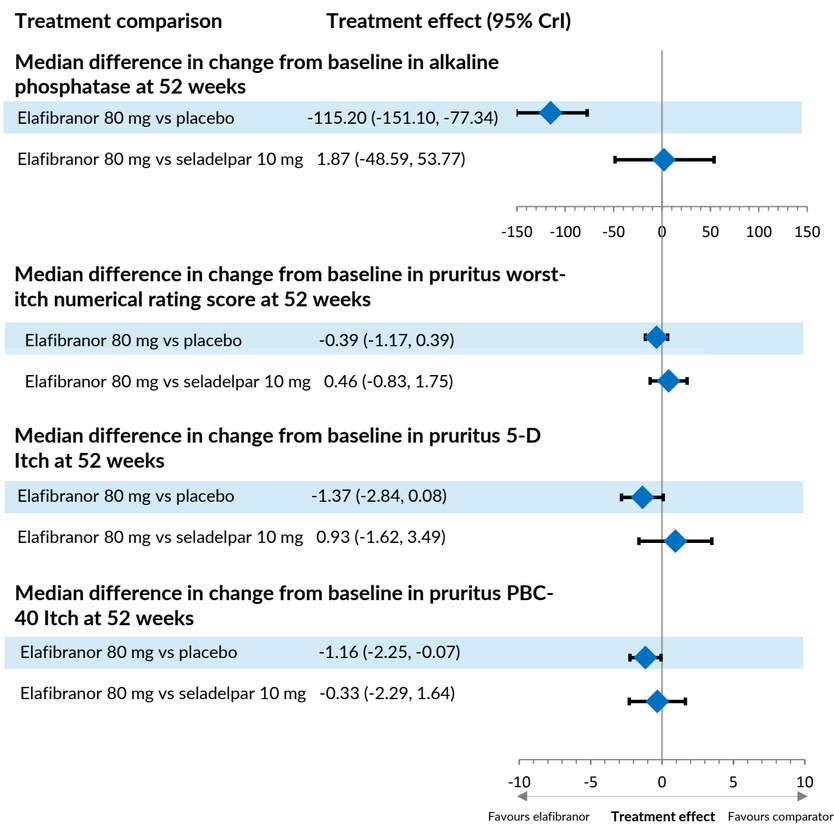
- Elafibranor had significantly greater odds (median odds ratio [95% credible interval (CrI)]) of achieving cholestasis response†, the primary endpoint in both studies, at Week 52 (13.02 [1.45-420.20]) versus seladelpar (**Figure 1A**).
  - A posterior probability of 0.991 confirmed that cholestasis response is more likely when patients are treated with elafibranor compared to seladelpar (**Table 1**).
- The remaining analyses did not identify significant differences between elafibranor and seladelpar (**Figure 1**):
  - Alkaline phosphatase normalisation (0.42 [0.00, 282.30]);
  - All-cause discontinuation (1.30 [0.25, 6.90]);
  - Pruritus as a treatment-emergent adverse event (0.73 [0.14, 3.81]);
  - Change from baseline in alkaline phosphatase (median difference (1.87 [-48.59, 53.77]);
  - Change from baseline in pruritus using the worst-itch numerical rating score (0.46 [-0.83, 1.75]), 5-D Itch (0.93 [-1.62, 3.49]), and PBC-40 Itch (-0.33 [-2.29, 1.64]).
- Model summary statistics and posterior probabilities for whether outcomes were more favourable with elafibranor than placebo and seladelpar are shown in **Table 1**.

Figure 1. NMA base-case results

1A. Odds ratios for NMA binary outcomes



1B. Median difference in change from baseline* for NMA continuous outcomes



†Cholestasis response was defined as an alkaline phosphatase level of less than or equal to 1.67 times the upper limit of the normal range, with a reduction of 15% or more from baseline, and total bilirubin levels within the normal range.
*Least-square mean change from baseline data was used for all continuous outcomes.

Table 1. NMA base-case summary statistics

Analysis	Between-study standard deviation on mean difference or odds ratio scale‡	Total residual deviance	Posterior probability of elafibranor being preferred to placebo	Posterior probability of elafibranor being preferred to seladelpar
Cholestasis response†	0.301	3.495	1.000	0.991
Alkaline phosphatase normalisation	0.301	3.851	0.999	0.380
All-cause discontinuation	0.194	3.430	0.586	0.368
Pruritus as a treatment-emergent adverse event	0.293	3.413	0.816	0.649
Change from baseline in alkaline phosphatase	11.810	3.333	1.000	0.472
Change from baseline in worst-itch numerical rating score	0.205	3.365	0.850	0.236
Change from baseline in 5-D Itch	0.366	3.344	0.969	0.233
Change from baseline in PBC-40 Itch	0.273	3.347	0.980	0.642

†Cholestasis response was defined as an alkaline phosphatase level of less than or equal to 1.67 times the upper limit of the normal range, with a reduction of 15% or more from baseline, and total bilirubin levels within the normal range.
‡Between-study standard deviation on the mean difference scale was used for continuous outcomes, while the odds ratio scale was used for binary outcomes

CONCLUSIONS

- The NMA indicates that cholestasis response is significantly more likely in patients treated with elafibranor than seladelpar, while no significant differences were identified between the treatments for the remaining outcomes.
- Results from the NMA can be used to inform comparative clinical efficacy and safety of elafibranor and seladelpar by healthcare decision-makers.
- A key limitation of the analysis is the relatively short duration of the ELATIVE and RESPONSE trials, which may not fully reflect the progressive, long-term nature of PBC and its associated complications.

Abbreviations CrI – credible interval; mg – milligram; NMA: network meta-analysis; PBC: primary biliary cholangitis

Footnotes †Cholestasis response was defined as an alkaline phosphatase level of less than or equal to 1.67 times the upper limit of the normal range, with a reduction of 15% or more from baseline, and total bilirubin levels within the normal range

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