Efficacy and Safety of Seladelpar vs. Elafibranor in Patients with Primary Biliary Cholangitis: A Matching-Adjusted Indirect Comparison (MAIC)

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Conclusion

- Seladelpar demonstrated overall numerically better biochemical efficacy and improved safety compared to elafibranor using a robust MAIC approach; however, statistical significance was not achieved

Plain language summary

- Primary biliary cholangitis (PBC) is a rare, chronic autoimmune liver disease marked by slow progression. PBC can cause the gradual destruction of intrahepatic bile ducts, followed by periportal inflammation and cholestasis
- Seladelpar and elafibranor are two emerging treatments for second-line PBC treatment. Both interventions have demonstrated substantial efficacy in the Phase III studies RESPONSE and ELATIVE, respectively
- Seladelpar was numerically better than elafibranor in most results, including reduction in alkaline phosphatase (ALP) levels and in achieving ALP normalization
- Moreover, treatment with seladelpar was linked to fewer adverse events, such as a lower incidence of pruritus and treatment discontinuations
- Overall, seladelpar exhibited a favorable efficacy and safety profile
- Further long-term trials are needed for more robust head-to-head comparisons to inform future clinical decision-making

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Introduction

- Primary biliary cholangitis (PBC) is a rare, cholestatic, and chronic autoimmune disease of the liver that results in the gradual destruction of intrahepatic bile ducts followed by periportal inflammation and cholestasis[1,2,3]
- Seladelpar[4] and elafibranor[5] are recently approved second-line treatments for PBC, both improving alkaline phosphatase (ALP) levels. However, only seladelpar significantly improves pruritus based on the pivotal studies (RESPONSE and ELATIVE, respectively) for each agent
- Several network meta-analyses (NMAs) have been conducted recently to compare the interventions; however, substantial differences in key effect modifiers and cut-off values across the trials render population-adjusted methods, such as matching adjusted indirect comparison (MAIC) preferable, consistent with the recommendations outlined in NICE TSD 18[6]
- An indirect treatment comparison (ITC) of the biochemical efficacy and safety was conducted in adult PBC patients using data from the RESPONSE and ELATIVE trials

Methods

- The clinical systematic literature review identified two Phase III randomized controlled trials (RCTs), RESPONSE[4] and ELATIVE[5], which evaluated the efficacy and safety of seladelpar 10 mg and elafibranor 80 mg, respectively, at 12 months **(Figure 1)**
- Due to substantial heterogeneity in effect modifiers, biochemical response thresholds, and placebo responses among trials **(Table 1)**, an anchored MAIC was performed following the NICE TSD 18 guidance[6]
- Individual-level data from RESPONSE were adjusted for four key effect modifiers (age, cirrhosis, bilirubin, and ALP levels) to match ELATIVE baseline characteristics **(Table 2).** The selection of effect modifiers was based on a comprehensive approach, incorporating previous NICE technology appraisal[7], targeted literature review[8,9] and clinical expert validation
- Binary biochemical efficacy endpoints of ALP normalization and the composite biochemical response **(Figure 2)** were recalculated to account for differences in ULN thresholds for ALP and total bilirubin. Additional efficacy comparison involved ALP change from baseline, which is not sensitive to normal range differences
- Both trials evaluated pruritus in moderate-to-severe subgroup (Numerical rating scale/NRS≥4); however, only seladelpar demonstrated a significant improvement in pruritus compared to elafibranor. Further, the lack of subgroup-specific baseline data in the ELATIVE trial limited the ability to include this outcome in the MAIC

Figure 1. Flow of studies in the SLR

ITC, Indirect treatment comparison; SLR, Systematic Literature Review

Table 1. Population characteristics reported across the trials

Population characteristics	ELATIVE[a]		RESPONSE[b]	
Intervention group	Elafibranor 80 mg (N=108)	Placebo (N=53)	Seladelpar 10 mg (N=128)	Placebo (N=65)
Mean age, years (SD)	57.5 (8.4)	56.4 (9.3)	56.6 (10.0)	57.0 (9.2)
Concurrent UDCA no. (%)	102 (94.0)	51 (96.0)	120 (93.7)	61 (93.8)
Female no. (%)	102 (94.0)	52 (98.0)	123 (96.1)	60 (92.3)
Race or ethnic group (White) no. (%)	101 (94.0)	46 (87.0)	114 (89.1)	56 (86.2)
Time since diagnosis, years	7.9 (5.9)	8.3 (6.8)	8.2 (6.7)	8.6 (6.5)
Baseline ALP mean U/L (SD)	321.3 (121.9)	323.1 (198.6)	314.6 (123.0)	313.8 (117.7)
Mean total bilirubin level-µmol/liter (SD)*	9.7 (5.1)	9.4 (5.0)	13.1 (5.1)	12.7 (5.1)
Cirrhosis at baseline-no. (%)*	9 (8.3)	7 (13.2)	18 (14.1)	9 (13.8)
Mean total aspartate aminotransferase-U/L (SD)	45.0 (24.2)	47.2 (32.8)	39.6 (16.1)	41.7 (16.0)
Mean total alanine aminotransferase-U/L (SD)	49.3 (29.4)	50.3 (38.7)	47.4 (23.5)	48.2 (22.8)
Mean total WI-NRS score (SD)	3.3 (2.8)	3.2 (2.9)	3.0 (2.8)**	3.0 (3.0)**
Mean total Liver stiffness Mean-kPa (SD)	9.9 (7.8)	10.7 (8.9)	9.8 (6.2)	8.7 (4.2)

ALP, Alkaline phosphatase; kPa, Kilopascal; SD, Standard deviation; UDCA, Ursodeoxycholic Acid; U/L, Units per Liter; ULN, Upper limit of normal; WI-NRS, Worst itch numeric rating scale; *Heterogeneous effect modifiers; **Pruritus NRS score
[a]The ULN for ALP level is 104 U/L for women and 129 U/L for men; The ULN for the total bilirubin level is 20.5 µmol/L for men and women
[b]The ULN for ALP level is 116 U/L in men and women; The ULN for the total bilirubin level is 18.8 µmol/L for men and women

Figure 2. Definitions for efficacy endpoints

- Safety was compared based on the incidence of overall treatment emergent adverse events (TEAEs), pruritus as a TEAE, and all-cause discontinuations
- Several sensitivity analyses were conducted, including an unanchored MAIC for the composite response outcome, which adjusts for population imbalances between treatments without relying on a common comparator

Table 2. Baseline covariates prior and post-matching; primary matching set

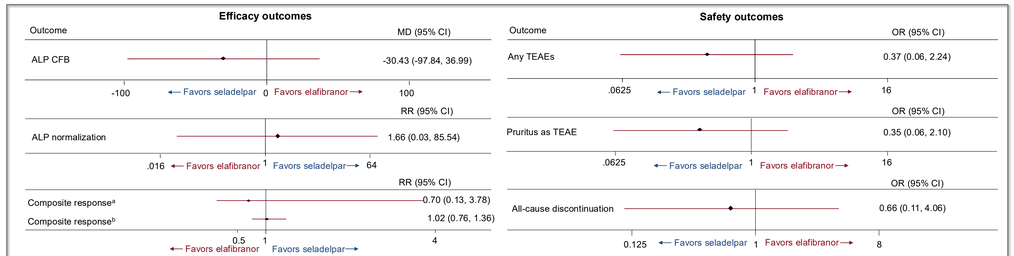
Variable	ELATIVE Raw	RESPONSE Raw	RESPONSE Adjusted*	
	N=161	N=193	N=193[a]	N=171[b] (Evaluable)**
Age, years (Mean±SD)	57.10 ± 8.70	56.73 ± 9.79	57.10 ± 8.72	57.10 ± 8.73
Cirrhosis (%)	10	14	10	10
Bilirubin, µmol/L (Mean±SD)	9.60 ± 5.10	12.83 ± 5.13	9.60 ± 5.11	9.60 ± 5.12
ALP, U/L (Mean±SD)	321.90 ± 150.90	314.30 ± 121.90	321.90 ± 151.29	321.90 ± 151.35

ALP, Alkaline phosphatase; N, Sample size; SD, Standard deviation, *Individual-level data from RESPONSE were adjusted for four key effect modifiers to match ELATIVE baseline characteristics; **Evaluable (sample size or population) refers to the number of participants for whom the outcome was measured in each intervention group; [a]For binary outcomes; [b]For continuous outcomes

Results

- Seladelpar showed numerically better results for ALP normalization, and greater reduction in ALP levels from baseline, with a mean difference of -30.43 U/L relative to elafibranor, while a numerically lower effect was observed for the composite endpoint using placebo as a common comparator
- It should be noted that any ITC for composite response involving elafibranor using placebo as a common comparator may be unreliable, given the different placebo response rates observed in the ELATIVE and RESPONSE trials, respectively (3.8% vs. 20.0%)
- Using the unanchored MAIC approach, seladelpar demonstrated a numerically higher composite response than elafibranor
- The odds of experiencing any TEAE, pruritus as a TEAE, and all-cause discontinuation were lower with seladelpar, with an odds ratio of 0.37, 0.35, and 0.66, respectively **(Figure 3)**
- The results for sensitivity analyses were aligned with the base case results for all the efficacy and safety outcomes **(Table 3)**

Figure 3: Forest plot of MAIC results for comparison between seladelpar 10 mg vs. elafibranor 80 mg



[a]Anchored (placebo as common comparator); [b]Unanchored (without common comparator); ALP, Alkaline phosphatase; CFB, Change from baseline; CI, Confidence interval; MAIC, Matching adjusted indirect comparison; MD, Mean difference; OR, Odds ratio; RR, Risk ratio; TEAE, Treatment-emergent adverse event; In the ELATIVE trial, the primary analysis was based on data from the double-blind period, with efficacy end points assessed at week 52; safety analyses included data up to 104 weeks; In the RESPONSE trial, all the efficacy and safety endpoints were assessed at 52 weeks

Table 3: Sensitivity analyses results for comparison between seladelpar 10 mg vs. elafibranor 80 mg

Efficacy outcomes	Risk Difference - Anchored MAIC	Bayesian NMA (Informative prior: Specific for Biological markers)	Unanchored MAIC
	RD (95%CI)	RR (95% CrI)	RR (95% CI)
ALP normalization	0.05 (-0.04, 0.15)	1.53 (0.01, 204.6)	--
Composite response	-0.01 (-0.19, 0.17)	0.68 (0.16, 2.15)	1.02 (0.76,1.36)
ALP CFB	--	-7.94 (-47.64, 38.01)	--

Safety outcomes	Bayesian NMA (Turner prior: Specific for adverse events)
	OR (95%CrI)
Any TEAE	0.42 (0.04, 4.87)
Pruritus	0.37 (0.04, 3.02)
All-cause discontinuation	0.57 (0.06, 5.78)

ALP, Alkaline phosphatase; CFB, Change from baseline; CI, Confidence interval; CrI, Credible interval; MAIC, Matching adjusted indirect comparison; NMA, Network meta-analysis; OR, Odds ratio; RD, Risk difference; RR, Risk ratio; TEAE, Treatment-emergent adverse event

Limitations

- The small number of studies included in the network (n=2) and the heterogeneity in effect modifiers and outcome definitions (ULN cut-off values), limited the use of conventional ITC approaches
- MAIC cannot account for unmeasured or unobservable differences between trials, which may still bias results despite matching. Moreover, extreme weights assigned during matching can reduce the effective sample size and limit statistical power, making it more difficult to detect meaningful differences between treatment