Non-invasive tests for liver fibrosis are stable in patients with primary biliary cholangitis with two years of treatment with elafibranor

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KEY LEARNINGS

With two years of elafibranor treatment, predictors of liver fibrosis remained stable in patients with PBC.

BACKGROUND

- Primary biliary cholangitis (PBC) is a rare, cholestatic liver disease that causes progressive destruction of interlobular bile ducts, resulting in biliary fibrosis.[1,2]
- Liver stiffness measurement (LSM) and Enhanced Liver Fibrosis (ELF) are non-invasive tests (NITs) for fibrosis.[3]
- The phase III ELATIVE® trial evaluated the efficacy and safety of elafibranor, a peroxisome proliferator-activated receptor (PPAR) agonist exerting effects on PPARα and PPARδ, approved for the treatment of PBC.[4-6]
- PPARα activation has been associated with positive effects on fibrosis.[7]

OBJECTIVE

- To assess the effect of elafibranor on NITs for fibrosis and biochemical markers in ELATIVE® to Week 104.

CONCLUSIONS

- This is the first study to present long-term data on markers of fibrosis with a PPAR agonist approved for PBC treatment.
- With two years of elafibranor treatment, NITs for liver fibrosis remained stable in patients with PBC.
- Improvement in some biomarkers of cholestasis and liver function (ALP and GGT) along with stabilisation of others (ALT and AST) was observed at Week 104.
- Biomarkers of disease progression (TB and ALB) were also stable at Week 104.
- These findings suggest that elafibranor may slow the worsening of fibrosis in patients with PBC.

METHODS

- In ELATIVE® (NCT04526665), patients were randomised 2:1 to once-daily elafibranor 80 mg or placebo to Week 52; patients could then enter an open-label extension (OLE) to receive elafibranor for up to five more years.[4]
- The proportions of patients with shifts above and below (suggesting worsening and improving, respectively) thresholds of 10 kPa in LSM and 9.8 in ELF are reported at Week 52 and Week 104.
- Proportions of patients achieving categorical change from baseline (CfB) using thresholds indicating worsening or improving outcomes are reported at Week 52 and Week 104: <−30%, ≥−30% to <−20%, ≥−20% to ≤20%, >20% to ≤30% and >30% in LSM, and <−0.5, ≥−0.5 to ≤0.5 and >0.5 in ELF.
- Data at Week 52 are reported for all patients with LSM and ELF recorded to Week 52; data at Week 104 are reported for elafibranor-randomised patients enrolled in the OLE, with LSM and ELF recorded to Week 104.
- CfB at Week 104 in alkaline phosphatase (ALP), total bilirubin (TB), albumin (ALB), alanine aminotransferase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT) were assessed in elafibranor-randomised patients with LSM recorded to Week 104.
- Safety of elafibranor was evaluated in patients with LSM and ELF to Week 104.

RESULTS

- Of 161 randomised patients, 134 had LSM and 134 had ELF recorded from baseline to Week 52 (elafibranor: n=90; placebo: n=44) in both subgroups.
- Among elafibranor-randomised patients enrolled in the OLE, 48 had LSM and 41 had ELF recorded from baseline to Week 104 at data cutoff.
- Baseline characteristics were generally similar across subgroups of patients with LSM and ELF available to different timepoints (Table 1).

Threshold changes in measures of fibrosis

- The proportions of patients shifting above and below 10 kPa in LSM at Week 52 were comparable between treatment groups (Figure 1).
- At Week 52, the proportions of patients shifting above the ELF threshold of 9.8 were similar between treatment groups, however a greater proportion of patients receiving elafibranor shifted below 9.8 compared with placebo (Figure 2).
- At Week 104, greater proportions of patients receiving elafibranor shifted below the thresholds than above, for both LSM and ELF (Figure 1, Figure 2).

Categorical changes in measures of fibrosis

- At Week 52, 81.2% elafibranor-randomised and 70.5% placebo-randomised patients had CfB ranging from ≤20% through <−30% in LSM, indicating similar or improved LSM; this proportion was sustained in elafibranor-randomised patients at Week 104 (77.1%) (Figure 3A).
- At Week 52, 80.0% elafibranor-randomised and 79.5% placebo-randomised patients had CfB ranging from ≤0.5 through <−0.5 in ELF, indicating similar or improved ELF; this proportion was sustained in elafibranor-randomised patients at Week 104 (73.2%) with 19.5% of patients showing improvement of <−0.5 (Figure 3B).

Changes in biomarkers of cholestasis and liver function

- In elafibranor-randomised patients with LSM recorded to Week 104, mean CfB in ALP and GGT at Week 104 were −124.0 U/L and −25.1 U/L, respectively. TB, ALT, AST and ALB were relatively stable (Figure 4).

Safety

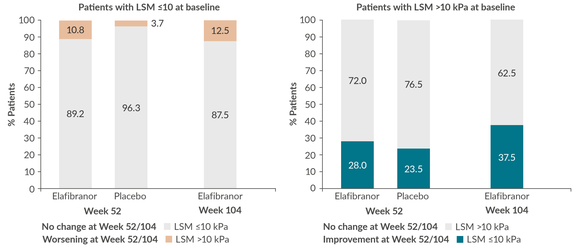
- Elafibranor was well tolerated in patients with LSM and ELF recorded to Week 104; no new safety signals emerged in patients completing 104 weeks of treatment, consistent with the safety profile during the 52-week double-blind period.[4]

Table 1. Baseline characteristics for patients with LSM and ELF recorded from baseline to Week 52 and Week 104

	LSM to Week 52		ELF to Week 52		LSM to Week 104	ELF to Week 104
	Elafibranor n=90	Placebo n=44	Elafibranor n=90	Placebo n=44	Elafibranor n=48	Elafibranor n=41
Age, years, mean (SD)	56.6 (8.4)	57.3 (9.4)	56.5 (8.1)	56.1 (9.1)	57.8 (7.8)	57.1 (7.4)
Sex, female, n (%)	85 (94.4)	43 (97.7)	84 (93.3)	43 (97.7)	45 (93.8)	38 (92.7)
Race, White, n (%)	84 (93.3)	38 (86.4)	83 (92.2)	38 (86.4)	45 (93.8)	38 (92.7)
Time since diagnosis, years, mean (SD)	7.7 (5.6)	8.7 (7.2)	7.5 (5.0)	8.5 (7.3)	8.6 (5.8)	8.7 (5.8)
LSM, kPa, mean (SD)	9.4 (7.7)	11.2 (9.4)	9.7 (7.8)[c]	10.1 (7.6)[d]	9.1 (4.0)	9.1 (4.0)[f]
ELF, mean (SD)	9.8 (1.0)[a]	9.8 (1.1)[b]	9.7 (1.0)	9.7 (0.9)	9.7 (0.9)[e]	9.7 (0.9)
ALB, g/L, mean (SD)	43.6 (2.8)	44.9 (3.2)	43.6 (2.7)	44.9 (3.2)	43.6 (3.1)	43.9 (3.1)
ALP, U/L, mean (SD)	323.9 (128.7)	331.6 (210.8)	324.0 (128.8)	332.9 (210.0)	312.2 (130.7)	316.0 (134.1)
ALT, U/L, mean (SD)	47.8 (26.4)	51.9 (41.0)	46.9 (28.0)	52.5 (40.5)	46.5 (29.8)	47.9 (31.2)
AST, U/L, mean (SD)	43.4 (22.4)	49.2 (35.0)	43.6 (24.3)	49.0 (35.0)	41.7 (24.5)	42.7 (26.0)
TB, µmol/L, mean (SD)	9.6 (4.8)	9.5 (5.0)	9.7 (4.9)	9.0 (4.7)	9.4 (4.7)	10.0 (4.9)
GGT, U/L, mean (SD)	205.1 (172.3)	221.3 (235.3)	210.0 (191.8)	227.6 (232.6)	194.8 (212.6)	208.0 (227.0)

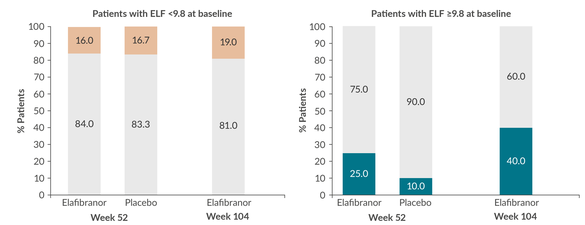
[a] n=88; [b] n=43; [c] n=87; [d] n=42; [e] n=47; [f] n=40.

Figure 1. Percentage of patients with shifts across the threshold of LSM 10 kPa from baseline to Week 52 and Week 104



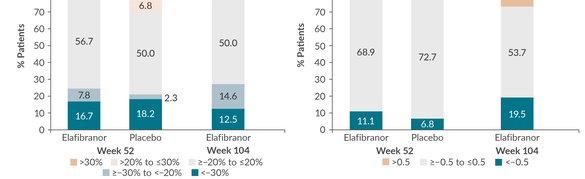
Evaluated in the subset of patients in ELATIVE® with LSM recorded from baseline to Week 52 (elafibranor: n=90; placebo: n=44) and from baseline to Week 104 (n=48). Patients with LSM from baseline to Week 52 with LSM ≤10 kPa at baseline: elafibranor: n=65; placebo: n=27. Patients with LSM from baseline to Week 52 with LSM >10 kPa at baseline: elafibranor: n=25; placebo: n=17. Patients with LSM from baseline to Week 104 with LSM ≤10 kPa at baseline: n=32. Patients with LSM from baseline to Week 104 with LSM >10 kPa at baseline: n=16.

Figure 2. Percentage of patients with shifts across the threshold of ELF 9.8 from baseline to Week 52 and Week 104



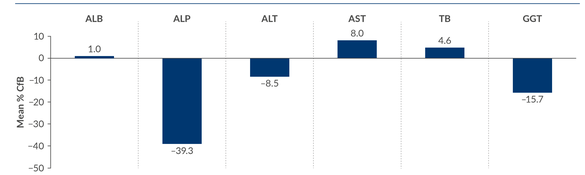
Evaluated in the subset of patients in ELATIVE® with ELF recorded from baseline to Week 52 (elafibranor: n=90; placebo: n=44) and from baseline to Week 104 (n=41). Patients with ELF from baseline to Week 52 with ELF <9.8 at baseline: elafibranor: n=50; placebo: n=24. Patients with ELF from baseline to Week 52 with ELF ≥9.8 at baseline: elafibranor: n=40; placebo: n=20. Patients with ELF from baseline to Week 104 with ELF <9.8 at baseline: n=21. Patients with ELF from baseline to Week 104 with ELF ≥9.8 at baseline: n=20.

Figure 3. Proportion of patients within categories of percentage change from baseline in NITs for fibrosis at Week 52 and Week 104



Changes from baseline to Week 52 are evaluated in the subset of patients in ELATIVE® with LSM or ELF recorded from baseline to Week 52 (elafibranor: n=90; placebo: n=44 for both subgroups); changes from baseline to Week 104 in LSM and ELF are evaluated in the subset of patients randomised to elafibranor in ELATIVE® and enrolled in the OLE, with LSM (n=48) or ELF (n=41) recorded from baseline to Week 104, respectively.

Figure 4. Percentage change from baseline in key biochemical markers of cholestasis and disease progression in elafibranor-randomised patients at Week 104



Changes in biomarkers are evaluated in the subset of elafibranor-randomised patients in ELATIVE® with LSM recorded from baseline to Week 104 (n=48).

Abbreviations **ALB:** albumin; **ALP:** alkaline phosphatase; **ALT:** alanine aminotransferase; **AST:** aspartate transaminase; **CfB:** change from baseline; **ELF:** Enhanced Liver Fibrosis; **GGT:** gamma-glutamyl transferase; **LSM:** liver stiffness measurement; **NIT:** non-invasive test; **OLE:** open-label extension; **PBC:** primary biliary cholangitis; **PPAR:** peroxisome proliferator-activated receptor; **TB:** total bilirubin.

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Author contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **All authors**; Drafting of the publication, or reviewing it critically for important intellectual content: **All authors**; Final approval of the publication: **All authors**.

Acknowledgments The authors thank all participants involved in the study as well as the investigators and research staff in participating institutions.

Disclosures **MJM:** Received grants from Cymabay, GENFIT, GlaxoSmithKline, Intercept, Ipsen, Mirum and Target RWE; Received consulting fees from Cymabay, GlaxoSmithKline, Intra Sana, Ipsen, Mallinckrodt and Mirum; Received support for attending meetings and/or travel from Cymabay, Ipsen and Mallinckrodt; **CL:** Received grants from Calliditas, CymaBay, Escient, Gilead, GlaxoSmithKline, Intercept, Ipsen, Kowa, Mirum, Target RWE and Zydus; **MGS:** Advisory role for Abbot, Advanz, Gilead, GlaxoSmithKline, Ipsen and Novo Nordisk; Received clinical trial funding from 89Bio, Altimmune, Ancella Health Inc., Bristol Myers Squibb, Calliditas, Celgene, CymaBay, Galectin Therapeutics, Gilead, GlaxoSmithKline, Intercept, Inventiva, Ipsen, Kowa, Madrigal, Merck, Novo Nordisk, Pfizer and Roche; **JMS:** Received grants from Boehringer Ingelheim, Gilead and Siemens Healthcare GmbH; Received consulting fees from Albireo, Apollo Endosurgery, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Intercept, Ipsen, Inventiva, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi and Siemens Healthcare GmbH; Received payment or honoraria from Boehringer Ingelheim, Echosens, Madrigal, MedPublico GmbH and Novo Nordisk; Received support for attending meetings and/or travel from Gilead; Stockholder of AGED diagnostics and Hepta Bio; **MAH:** Received royalties or licenses from UpToDate; Received consulting fees from Ipsen; Received payment or honoraria from Advanz; Secretary for the British Association for Study of the Liver (2020–2022); **CC:** Received grants from Arrow and Intercept; Received consulting fees from Calliditas, Cymabay, Intercept and Ipsen; Received support for attending meetings and/or travel from Biotest, Cymabay, Gilead, Intercept and Ipsen; **CLB:** Received grants from Calliditas, ChemoMab, COUR, Cymabay, Gilead, GlaxoSmithKline, Hanmi, Intercept, Ipsen, Mirum, Novartis, Novo Nordisk, Pliant Therapeutics, Viking and Zydus; Received consulting fees from ChemoMab, Cymabay, GlaxoSmithKline, Ipsen, Mirum, NGM Bio and Pliant Therapeutics; **NA**, **VC**, **HGdS:** Employees of Ipsen; **CR:** Statistical consultant to Ipsen; **KVK:** Received grants from Boston Scientific, Corcept, CymaBay, GENFIT, Gilead, GlaxoSmithKline, Hanmi, Intercept, Ipsen, Janssen, Madrigal, Mirum, Novo Nordisk, NGM Bio, Pfizer, Pliant Therapeutics, Terns, Viking, Zydus and 89bio Inc.; Received royalties or licenses from UpToDate; Received consulting fees from CymaBay, Enanta, GENFIT, Gilead, HighTide, Inipharm, Intercept, Ipsen, Madrigal, Mirum, NGM Bio, Pliant Therapeutics, Pfizer, Protagonist, Zydus and 89bio Inc.; Received payment or honoraria from AbbVie, Gilead and Intercept; Received payment for expert testimony from the US Department of Justice; Participant on a Data Safety Monitoring Board or Advisory Board for CTI, Medpace, Labcorp and Worldwide Clinical Trials; Stockholder in Inipharm; Receipt of equipment, materials, drugs, medical writing, gifts or other services from Velacur.

Medical writing support The authors thank Sneha Krishnamurthy, MSc, Aditi Mehta, MSc, and Oliver Palmer, BSc (Hons), of Costello Medical, UK, for providing medical writing support, and the Costello Medical Creative team for design support, which was sponsored by Ipsen in accordance with Good Publication Practice guidelines.

Presented at EASL 2025 | Amsterdam, The Netherlands | 7–10 May 2025

Secondary analyses and publication development were sponsored by Ipsen. This study was sponsored by Ipsen/GENFIT.