Elafibranor improves fatigue versus placebo in patients with primary biliary cholangitis, with limited correlation with pruritus: Analyses from the phase III ELATIVE® trial

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KEY LEARNINGS

Improvements in fatigue and pruritus with elafibranor treatment can occur independently of each other in patients with PBC.

BACKGROUND

- Fatigue and pruritus are common symptoms in primary biliary cholangitis (PBC). While their underlying mechanisms are unclear, it has been hypothesised that fatigue may be exacerbated by pruritus in some patients.
- In the phase III ELATIVE® trial (NCT04526665) elafibranor, a peroxisome proliferator activated receptor (PPAR) agonist exerting effects on both PPARα and PPARδ, significantly improved prognostic biomarkers of cholestasis in PBC.[1]

OBJECTIVE

- To report the impact of elafibranor versus placebo on fatigue to Week 52 in ELATIVE®, as well as evaluate the association between fatigue and pruritus.

CONCLUSIONS

- Treatment with elafibranor to Week 52 resulted in clinically meaningful improvements in fatigue, with greater improvements compared with placebo.
- Weak correlations between fatigue and pruritus PRO scores at baseline, and notably in changes to Week 52, suggest that elafibranor can improve these debilitating PBC symptoms independently of each other.
- Proteomic analyses from ELATIVE® offers insights into the mechanisms by which elafibranor may improve fatigue, potentially linked to the PPARα agonism effect on mitochondrial dysfunction [see **Poster LBP-025**].

METHODS

- In ELATIVE®, patients were randomised 2:1 to receive once-daily elafibranor 80 mg or placebo to Week 52.
- Fatigue was assessed via the Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a (PFSF 7a) and the PBC-40 Fatigue domain.
- Data are reported for patients with valid fatigue data at baseline and at Week 52, and for the subgroup of patients with moderate-to-severe fatigue at baseline (defined as PFSF 7a score ≥60 or PBC-40 Fatigue domain score ≥29).
- Changes in PFSF 7a and the PBC-40 Fatigue domain were summarised from baseline to Week 52, with respect to mean scores, categorical changes, and minimal clinically important differences (MCIDs; PFSF 7a: improvements ≥3 points; PBC-40 Fatigue domain: improvements ≥5 points).
- Spearman's correlation coefficients were calculated between fatigue (PFSF 7a and PBC-40 Fatigue domain) and pruritus (PBC Worst Itch Numeric Rating Scale [WI NRS], 5-D Itch, and PBC-40 Itch domain) patient-reported outcomes (PROs) for scores at baseline and change from baseline to Week 52. Moderate-to-severe pruritus was defined as PBC WI NRS ≥4.
- Patients with missing fatigue data at baseline and/or Week 52 were excluded.

RESULTS

Improvements in fatigue with elafibranor to Week 52

- Of 161 patients randomised (elafibranor: n=108; placebo: n=53), 141 patients had valid fatigue data at baseline and Week 52 (elafibranor: n=95; placebo: n=46), of which 58 (elafibranor: n=42; placebo: n=16) and 79 (elafibranor: n=53; placebo: n=26) had moderate-to-severe fatigue at baseline according to PFSF 7a and the PBC-40 Fatigue domain, respectively (Table 1).
- Improvements in PFSF 7a and PBC-40 Fatigue domain scores from baseline to Week 52 were larger in patients receiving elafibranor versus placebo; more pronounced improvements were seen in patients with moderate-to-severe fatigue at baseline (Figure 1).
- In patients with moderate-to-severe fatigue at baseline, 18/42 (42.9%; PFSF 7a) and 12/53 (22.6%; PBC-40 Fatigue domain) patients receiving elafibranor improved to mild/normal fatigue versus 5/16 (31.3%; PFSF 7a) and 4/26 (15.4%; PBC-40 Fatigue domain) patients receiving placebo.
- In patients with moderate-to-severe fatigue at baseline, higher proportions receiving elafibranor achieved improvements ≥MCID to Week 52 versus placebo (Figure 2).

Weak correlations between fatigue and pruritus

- **At baseline**, fatigue and pruritus PRO scores had weak correlations in patients with moderate-to-severe fatigue at baseline (r=0.05–0.35), suggesting that, while both symptoms could co-exist, pruritus was not a main driver of fatigue.
  - The numbers of patients with moderate to severe fatigue and/or moderate-to-severe pruritus at baseline are shown in Figure 3.
- **Changes from baseline to Week 52** in fatigue and pruritus PRO scores did not demonstrate a strong correlation in all patients (r=0.08–0.26) and in patients with moderate-to-severe fatigue at baseline (r=0.21–0.33) receiving elafibranor or placebo. Similar results were observed for patients treated with elafibranor (r=<0.01–0.26 for all elafibranor patients; r=0.19–0.26 for elafibranor patients with moderate-to-severe fatigue at baseline), showcasing that both symptoms, pruritus and fatigue, improve independently of one another (Table 2).

Table 1. Baseline demographics and disease characteristics

	All patients		Moderate-to-severe fatigue at baseline			
			PFSF 7a		PBC-40 Fatigue domain	
	Elafibranor n=95	Placebo n=46	Elafibranor n=42	Placebo n=16	Elafibranor n=53	Placebo n=26
Age, mean (SD)	56.1 (8.3)	56.2 (9.3)	53.6 (7.4)	53.6 (9.9)	53.9 (7.7)	55.3 (10.3)
Sex, female, n (%)	89 (93.7)	45 (97.8)	39 (92.9)	16 (100.0)	49 (92.5)	25 (96.2)
Time since diagnosis, years, mean (SD)	7.7 (5.5)	8.5 (7.1)	6.7 (4.3)	5.3 (3.4)	6.9 (4.4)	6.5 (5.1)
ALP, U/L, mean (SD)	323.6 (126.8)	327.6 (206.9)	352.2 (165.2)	358.7 (300.7)	336.5 (152.9)	322.6 (239.2)
PFSF 7a score, mean (SD)	56.5 (11.3)	54.3 (11.5)	66.7 (4.7)	66.2 (3.7)	63.9 (7.3)	62.2 (5.9)
PBC-40 Fatigue domain score, mean (SD)	29.0 (11.3)	28.5 (12.1)	39.0 (6.1)	39.6 (7.9)	37.6 (6.2)	37.5 (6.8)

Figure 1. Mean change in (A) PFSF 7a and (B) PBC-40 Fatigue domain scores from baseline to Week 52

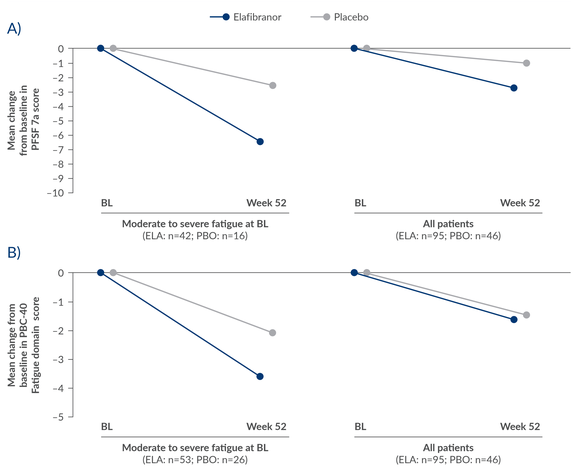

Figure 2. Proportion of patients with moderate-to-severe fatigue at baseline achieving ≥MCID at Week 52

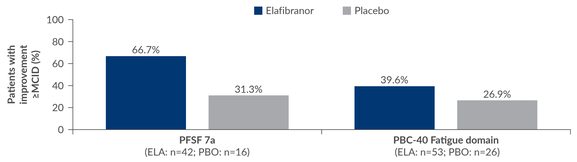

Figure 3. Distribution of patients at baseline with moderate-to-severe fatigue and/or moderate-to-severe pruritus and correlation coefficients between fatigue and pruritus PROs

A) PFSF 7a and PBC WI NRS

Moderate-to-severe pruritus and **normal/mild fatigue** n=21	Moderate-to-severe pruritus and fatigue n=37	**Normal/mild pruritus** and moderate-to-severe fatigue n=21

Spearman's correlation coefficients between fatigue (PFSF7a) and pruritus (WI NRS) PRO scores at baseline

	Spearman's correlation coefficient: No correlation 0.0 Weak 0.3 Moderate 0.7 Strong 1.0 Perfect correlation	ELA+PBO n
Patients with moderate-to-severe fatigue at baseline	0.05	58

B) PBC-40 Fatigue domain and PBC WI NRS

Moderate-to-severe pruritus and **normal/mild fatigue** n=13	Moderate-to-severe pruritus and fatigue n=45	**Normal/mild pruritus** and moderate-to-severe fatigue n=34

Spearman's correlation coefficients between fatigue (PBC-40 Fatigue domain) and pruritus (WI NRS) PRO scores at baseline

	Spearman's correlation coefficient: No correlation 0.0 Weak 0.3 Moderate 0.7 Strong 1.0 Perfect correlation	ELA+PBO n
Patients with moderate-to-severe fatigue at baseline	0.27	79

Moderate-to-severe fatigue was defined as PFSF 7a score ≥60 or PBC-40 Fatigue domain score ≥29. Moderate-to-severe pruritus was defined as PBC WI NRS ≥4. Correlations are defined as: <0.3=weak; ≥0.3–<0.7=moderate; ≥0.7–1.0=strong.

Table 2. Correlation coefficients between change from baseline in fatigue and pruritus PROs

ELA+PBO ELA

Fatigue PRO	Pruritus PRO	Spearman's correlation coefficient: No correlation 0.0 Weak 0.3 Moderate 0.7 Strong 1.0 Perfect correlation	ELA n	ELA+PBO n
All patients				
PBC-40 Fatigue domain	5-D Itch	0.26 0.26	95	141
PBC-40 Fatigue domain	PBC-40 Itch domain	0.10 0.12	95	141
PBC-40 Fatigue domain	PBC WI NRS	0.24 0.25	80	119
PFSF 7a	5-D Itch	0.14 0.16	95	141
PFSF 7a	PBC-40 Itch domain	<0.01 0.08	95	141
PFSF 7a	PBC WI NRS	0.18 0.20	80	119
Patients with moderate-to-severe fatigue at baseline				
PBC-40 Fatigue domain	5-D Itch	0.26 0.33	53	79
PBC-40 Fatigue domain	PBC-40 Itch domain	0.23 0.26	53	79
PBC-40 Fatigue domain	PBC WI NRS	0.24 0.27	41	63
PFSF 7a	5-D Itch	0.19 0.30	42	58
PFSF 7a	PBC-40 Itch domain	0.23 0.32	42	58
PFSF 7a	PBC WI NRS	0.21 0.22	31	44

Correlations are defined as: <0.3=weak; ≥0.3–<0.7=moderate; ≥0.7–1.0=strong.

Abbreviations **BL:** baseline; **ELA:** elafibranor; **MCID:** minimal clinically important difference; **PBC:** primary biliary cholangitis; **PBO:** placebo; **PFSF 7a:** PRO Measurement Information System Fatigue Short Form 7a; **PPAR:** peroxisome proliferator-activated receptor; **PRO:** patient-reported outcome; **PROMIS:** Patient-Reported Outcome Measurement Information System; **WI NRS:** Worst Itch Numeric Rating Scale.

References 1. Kowdley KV. N Engl J Med. 2024;390:795–805.

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