Efficacy and safety of elafibranor in primary biliary cholangitis: Results from the ELATIVE™ double-blind, randomized, placebo-controlled phase 3 trial


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Disclosures of the presenting author

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Background

• **Primary biliary cholangitis (PBC)** is a liver disease that mostly affects women over 40 years old

• People with PBC often have symptoms of itching and tiredness

Currently available medications:

<table>
<thead>
<tr>
<th>1st treatment option:</th>
<th>2nd treatment option:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ursodeoxycholic acid (UDCA)</td>
<td>obeticholic acid (OCA)</td>
</tr>
<tr>
<td>Up to 40% of people do not see an improvement</td>
<td>Over 50% of people do not see an improvement</td>
</tr>
<tr>
<td>3–5% are unable to take UDCA</td>
<td>Itching may get worse</td>
</tr>
</tbody>
</table>

• Elafibranor is a potential new medication for people with PBC

• In a previous clinical trial, elafibranor improved liver health and symptoms of itch

ELATIVE™ phase 3 trial objectives and design

ELATIVE™ aimed to:

• Find out **how well elafibranor works** in treating PBC in people who did not get better with current treatment (UDCA)
• Find out what the **side effects** of elafibranor might be

Recruitment

- Adults with PBC who did not get better with UDCA
  - 161 people in total

Optional extension

- Take elafibranor tablet once a day
- Take tablet with no medicine (placebo) once a day

Both groups also continued taking their current UDCA, unless they were unable to take it

First analysis of results at 1 year

- 108 people
- 53 people

People could choose to stay in the trial and continue to take elafibranor

- Up to 2 years
- Up to 5 years

PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid. Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.
Study outcomes

Liver health

- Alkaline phosphatase (ALP) and bilirubin are two substances found in the blood
- These help people understand how bad a person’s liver disease might be
- Higher amounts of these substances in the blood indicate worse disease

Itch

- People with PBC often have itchy skin
- We can measure how bad the itch is by using a questionnaire called PBC Worst Itch Numeric Rating Scale (NRS)
- Other questionnaires include the PBC-40 and 5-D Itch

Side effects

- The side effects of elafibranor treatment were tracked and recorded during the trial
Age, background, and health conditions were recorded for people taking part in the trial

- **Average age**: 58 years (108 people) vs. 56 years (53 people)
- **Sex**: 102 (94%) females vs. 52 (98%) females
- **Race**: 101 (94%) White vs. 46 (87%) White
- **Average time since PBC diagnosis**: 8 years (108 people) vs. 8 years (53 people)

### Health Conditions

- **People with ALP over 3 times the normal level**: 43 (40%) people vs. 20 (38%) people
- **People with bilirubin over the normal level**: 4 (4%) people vs. 2 (4%) people
- **People with relentless itch**: 44 (41%) people vs. 22 (42%) people

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*Defined as people with moderate-to-severe itch (PBC Worst Itch NRS score ≥4). ALP: alkaline phosphatase; NRS: numeric rating scale; PBC: primary biliary cholangitis. Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.*
The majority of people taking elafibranor had improved liver health after 1 year.

- ALP and bilirubin are substances in the blood used to measure liver health.
- Higher amounts indicate worse disease.
- More people taking elafibranor had lower levels of these substances after 1 year, which shows that their liver health was improving.

Note that a few people were unable to also take UDCA.
Only people taking elafibranor reached completely normal levels of ALP after 1 year

**Percentage of people with completely normal levels of ALP**

- **Elafibranor (N=108)**: 15%
- **Placebo (N=53)**: 0%

- Researchers also looked to see if ALP reached completely normal levels during the trial.
- Normal levels of ALP are what we expect to see in people without PBC.
- Only people who took elafibranor reached completely normal levels of ALP after 1 year.

Note that a few people were unable to also take UDCA.
Elafibranor greatly reduced levels of ALP – this effect was seen as early as 4 weeks of treatment, and lasted throughout the trial.

Researchers measured ALP regularly throughout the trial.

ALP dropped quickly in people taking elafibranor, which shows that liver health was improving after just 4 weeks of treatment.

Note that a few people were unable to also take UDCA.

Data are shown as mean ± SEM. ALP: alkaline phosphatase; SEM: standard error of the mean; UDCA: ursodeoxycholic acid. Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.
How researchers measured itch in ELATIVE

**PBC Worst-Itch NRS**
- Simple 1-question form that measures the intensity of itch
  - 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable)
  - Patients reported this information every day
  - Patients were asked to rate this score for the last 24 hours

**PBC-40 Itch Domain**
- Multi-question form that asks about the impact of itching on patients’ lives and was specifically designed and validated for PBC
  - Three-item questionnaire with each item scored from 1 to 5, higher scores indicating worse quality of life
  - Patients reported this information at each study visit
  - Patients were asked to rate this score for the last 4 weeks

**5-D Itch**
- Multi-question form that asks about the severity of itch and the impact of itching on patients’ lives
  - Questionnaire consisting of 5 domains (duration, degree, direction, disability, distribution) for a total score ranging from 5 (no itching/no effect) to 25 (most severe effect of itch on the 5 domains)
  - Patients reported this information at each study visit
  - Patients were asked to rate this score for the last 2 weeks

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5-D: 5-Dimensional; PBC: primary biliary cholangitis; WI-NRS: worst itch numerical rating score.
Differences in the PBC Worst Itch NRS questionnaire were not large enough to conclude that itch was improved.

- Researchers measured how bad people’s itch was using a questionnaire called PBC Worst Itch NRS.
- In people with relentless itch, according to this questionnaire, elafibranor did not reduce itch more than placebo (the difference between the two groups was not large enough to confidently say that elafibranor reduced itch).

Data are shown as LS mean ± 95% CI, for people with relentless itch (defined as people with moderate-to-severe itch at start of trial [PBC Worst Itch NRS score ≥4]). CI: confidence interval; LS: least square; NRS: numeric rating scale; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid. Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.

Note that a few people were unable to also take UDCA.
The PBC-40 questionnaire suggested that elafibranor may improve symptoms of itch after 1 year.

Data are shown as LS mean ± 95% CI, for people with relentless itch (defined as people with moderate-to-severe itch at start of trial [PBC Worst Itch NRS score ≥4]). 5-D: 5-Dimensional; CI: confidence interval; LS: least square; NRS: numeric rating scale; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid. Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.

- Two other questionnaires (PBC-40 and 5-D Itch) were also used to measure itch.
- In people with relentless itch, the PBC-40 questionnaire suggested that elafibranor may improve symptoms of itch after 1 year.

Note that a few people were unable to also take UDCA.
The 5-D Itch questionnaire also suggested that elafibranor may improve symptoms of itch after 1 year.

Data are shown as LS mean ± 95% CI, for people with relentless itch (defined as people with moderate-to-severe itch at start of trial [PBC Worst Itch NRS score ≥4]). 5-D: 5-Dimensional; CI: confidence interval; LS: least square; NRS: numeric rating scale; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid. Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.

- In people with relentless itch, the 5-D Itch questionnaire also suggested that elafibranor may improve symptoms of itch after 1 year.
The most common side effects of elafibranor in the trial were gut-related

<table>
<thead>
<tr>
<th>Side effects</th>
<th>108 people took elafibranor</th>
<th>53 people took placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with any side effect</td>
<td>104 (96.3%)</td>
<td>48 (90.6%)</td>
</tr>
<tr>
<td>Stomach pain(^a)</td>
<td>12 (11.1%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (11.1%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (11.1%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (11.1%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>People with any treatment-related side effect</td>
<td>42 (38.9%)</td>
<td>21 (39.6%)</td>
</tr>
<tr>
<td>People with any serious side effect</td>
<td>11 (10.2%)</td>
<td>7 (13.2%)</td>
</tr>
<tr>
<td>People who stopped treatment due to a side effect</td>
<td>11 (10.2%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>2 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Deaths related to treatment(^b)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Including abdominal pain, lower abdominal pain, and upper abdominal pain; \(^b\) As determined by the trial investigators and confirmed by an independent group of researchers that reviewed trial side effects. Specific side effects displayed are only those occurring in over 10% of people treated with elafibranor, and which occurred in over 1% more people taking elafibranor than placebo.

This table shows the number of people who had certain side effects.

Treatment-related side effects are side effects that are likely to have been caused by the medication given in the trial.

Serious side effects either:
- Result in death
- Are life threatening
- Require staying in hospital
- Lead to ongoing or major disability
Elafibranor treatment resulted in **improvement in liver health**

Elafibranor may **improve symptoms of itchy skin**, according to the PBC-40 Itch and 5-D Itch questionnaires

The most common side effects of elafibranor were **stomach pain, diarrhea, nausea, and vomiting**

**Conclusions**

If approved for use, **elafibranor could be used to treat PBC** in people who did not see an improvement with current treatment (UDCA)
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AUTHOR CONTRIBUTIONS

- All authors provided substantial contributions to study conception and design; substantial contributions to analysis and interpretation of the data; drafting the article or revising it critically for important intellectual content; and final approval of the version of the article to be published.

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These Principal Investigators screened at least one patient for the trial. Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.
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A plain language summary of the full paper is available in its supplementary appendix

Full paper at:
Thank you!

Full paper