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

ELATIVE™

Plain language version

AASLD The Liver Meeting® Nov. 10-14, 2023

Christopher L. Bowlus,[1] Kris V. Kowdley,[2,3] Cynthia Levy,[4] Ulus Akarca,[5] Mario Reis Alvares-da-Silva,[6] Pietro Andreone,[7] Marco Arrese,[8] Christophe Corpechot,[9] Sven Francque,[10,11] Michael A. Heneghan,[12] Pietro Invernizzi,[13,14] David Jones,[15] Frederik C. Kruger,[16,17] Eric Lawitz,[18] Marlyn J. Mayo,[19] Mitchell L. Shiffman,[20] Mark G. Swain,[21] José Miguel Valera,[22] Victor Vargas,[23] John M. Vierling,[24] Alejandra Villamil,[25] Carol Addy,[26] Julie Dietrich,[26] Jean-Michel Germain,[27] Sarah Mazain,[28] Dragutin Rafailovic,[27] Bachirou Taddé,[27] Benjamin Miller,[29] Jianfen Shu,[29] Claudia O. Zein,[29] Jörn M. Schattenberg,[30] and the ELATIVE™ Study Group

Presented at The Liver Meeting, AASLD 2023 | Boston, MA, USA | November 10–14 2023

#48490

Disclosures of the presenting author

Christopher L. Bowlus	Received grants from Boston Scientific, Bristol Myers Squibb, Calliditas, Cara Therapeutics, ChemoMab, COUR Pharmaceuticals, CymaBay, Gilead, GlaxoSmithKline, Hanmi, and Ipsen Received consulting fees from CymaBay, GlaxoSmithKline, Invea, Ipsen, and Mirum

Background

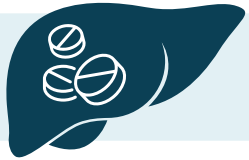
- **Primary biliary cholangitis (PBC)** is a liver disease that mostly affects women over 40 years old[1–3]

  - People with PBC often have symptoms of **itching** and **tiredness**[1]

Currently available medications:[2]

1st treatment option: ursodeoxycholic acid (UDCA)	2nd treatment option: obeticholic acid (OCA)
Up to **40%** of people do not see an improvement[4]	Over **50%** of people do not see an improvement[6]
3–5% are unable to take UDCA[5]	**Itching** may get worse[6]

- **Elafibranor** is a potential new medication for people with PBC[7]
- In a **previous clinical trial**, elafibranor improved liver health and symptoms of itch[7]



1. EASL. J Hepatol 2017;67:145–172; 2. Lindor KD. et al. Hepatology 2019;69:394–419; 3. Lv T. et al. J Gastroenterol Hepatol 2021;36:1423–1434; 4. Corpechot C. et al. Hepatology 2008;48:871–877; 5. Invernizzi P. et al. Dig Liver Dis 2017;49:841–846; 6. Nevens F. et al. N Engl J Med 2016;375:631–643; 7. Schattenberg JM. et al. J Hepatol 2021;74:1344–1354. OCA: obeticholic acid; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid.

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

Core trial
People randomly split into two groups

Take elafibranor tablet once a day — 108 people

Take tablet with no medicine (placebo) once a day — 53 people

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

Optional extension

Take elafibranor tablet once a day

First analysis of results at 1 year

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

1 year | Up to 2 years | Up to 5 years

PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid.

Study outcomes

ELATIVE™

AASLD The Liver Meeting® Nov. 10-14, 2023

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

5-D: 5-Dimensional; ALP: alkaline phosphatase; NRS: numeric rating scale; PBC: primary biliary cholangitis.

Age, background, and health conditions were recorded for people taking part in the trial

ELATIVE™

AASLD The Liver Meeting® Nov. 10-14, 2023

108 people took elafibranor | 53 people took placebo

Average age

58 years | 56 years

Sex

102 (94%) females | 52 (98%) females

Race

101 (94%) White | 46 (87%) White

Average time since PBC diagnosis

8 years | 8 years

People with ALP over 3 times the normal level

43 (40%) people | 20 (38%) people

People with bilirubin over the normal level

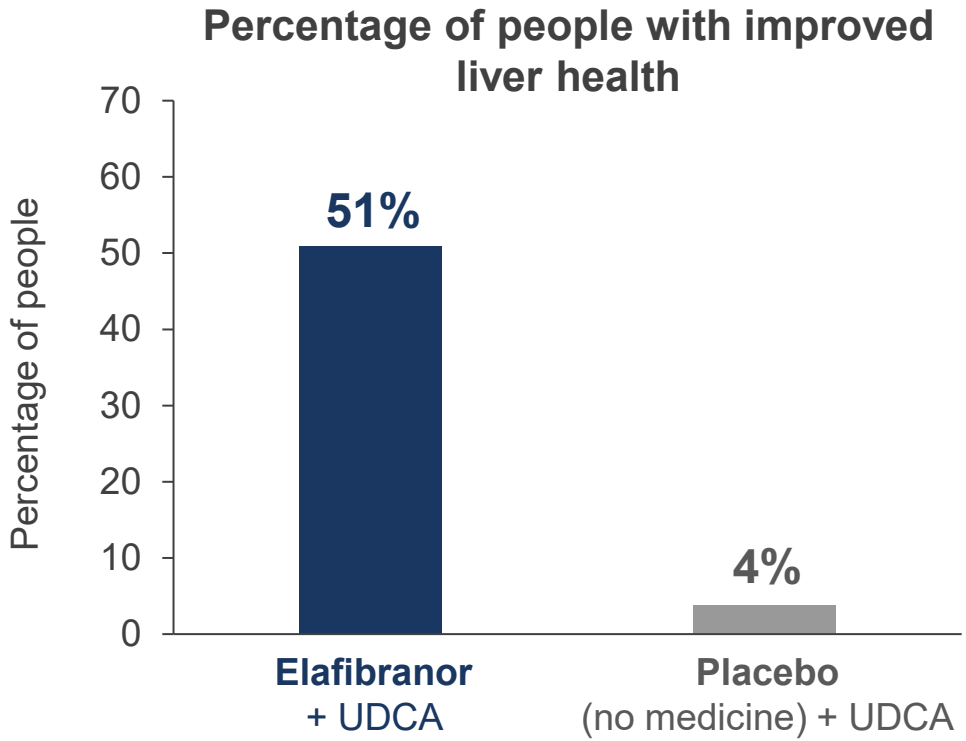
4 (4%) people | 2 (4%) people

People with relentless itch[a]

44 (41%) people | 22 (42%) people

[a]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.

The majority of people taking elafibranor had improved liver health after 1 year

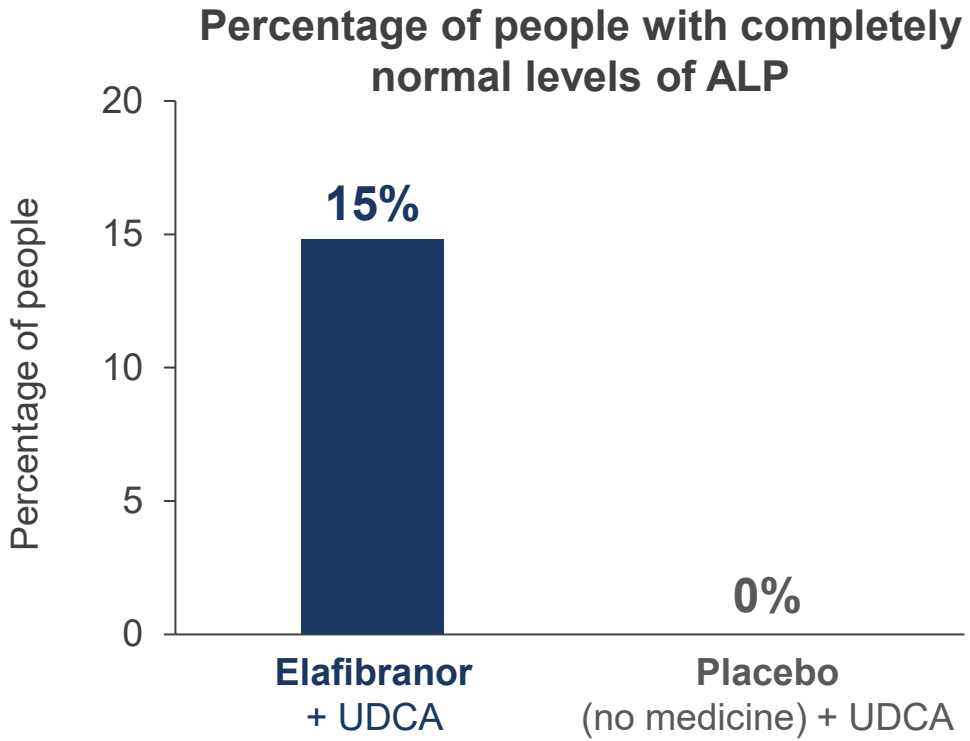


- ALP and bilirubin are substances in the blood used to measure liver health
- Higher amounts indicate worse disease
- **More people taking elafibranor had lower levels of these substances after 1 year, which shows that their liver health was improving**

Note that a few people were unable to also take UDCA

ALP: alkaline phosphatase; 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.*

Only people taking elafibranor reached completely normal levels of ALP after 1 year

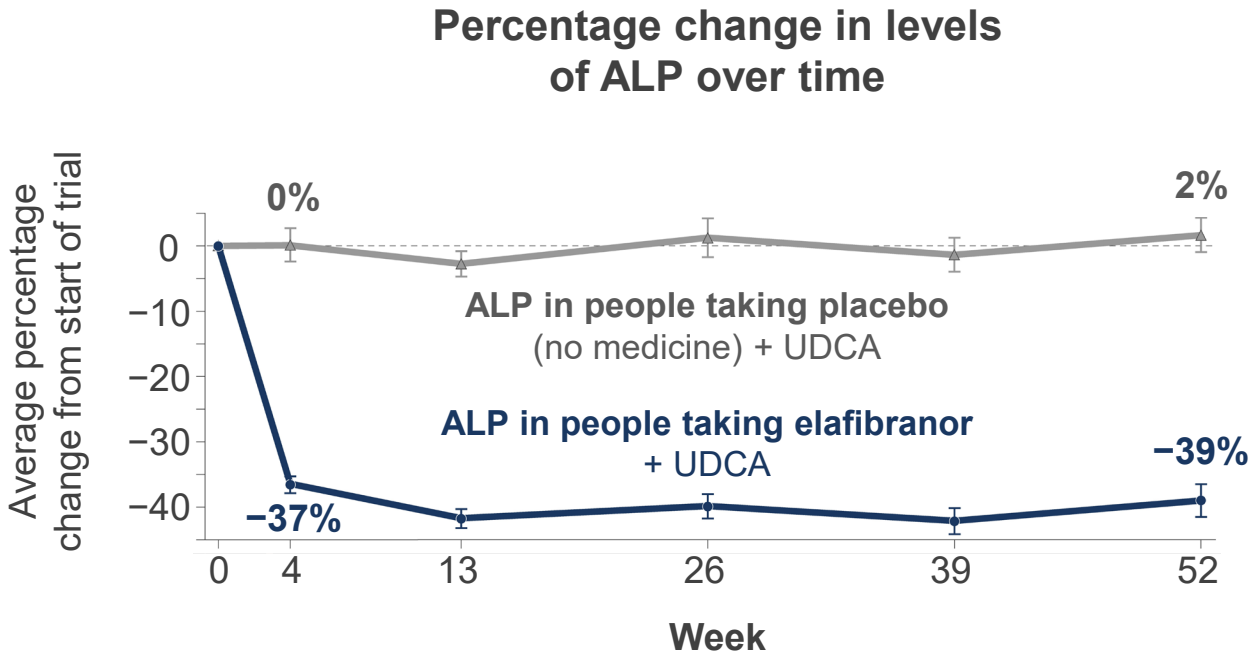


- Researchers also looked to see if ALP reached completely normal levels during the trial
- Normal levels of ALP are what we expect to see in people without PBC
- **Only people who took elafibranor reached completely normal levels of ALP after 1 year**

Note that a few people were unable to also take UDCA

ALP: alkaline phosphatase; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid.

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.*

Plain language version
#48490, AASLD 2023

How researchers measured itch in ELATIVE

PBC Worst-Itch NRS[1]

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[2]

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[3]

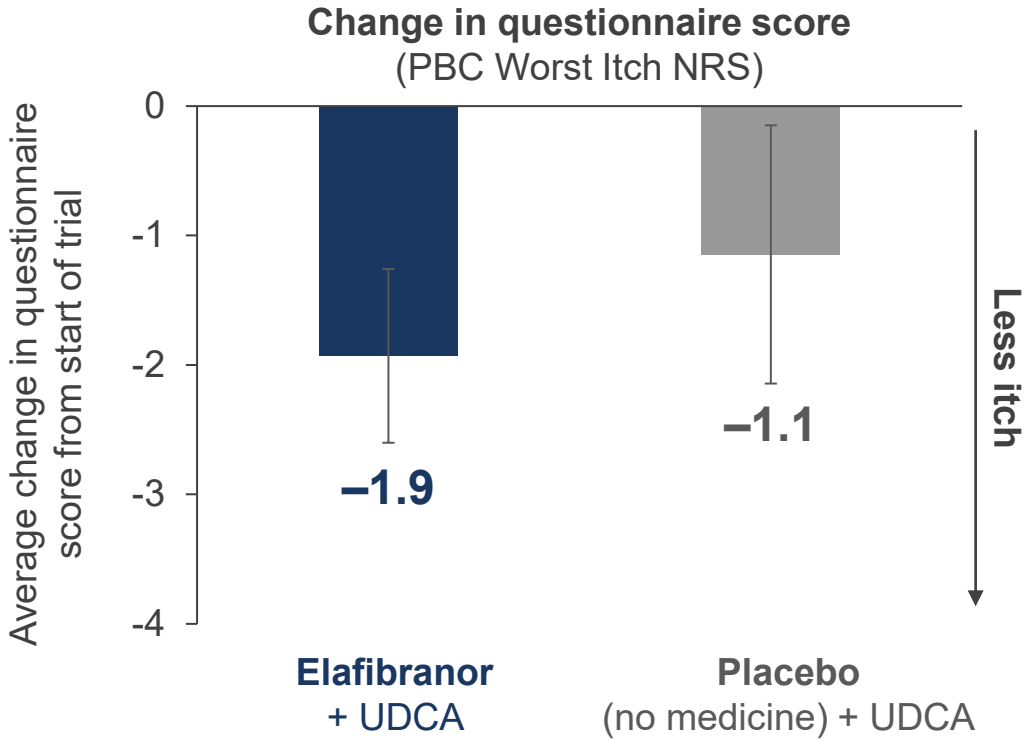
Multi-question form that asks about the severity of itch and the impact of itching on patients' lives

- 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

5-D: 5-Dimensional; PBC: primary biliary cholangitis; WI-NRS; worst itch numerical rating score.

1. Vernon MK et al. J Patient Rep Outcomes 2021;5:134; **2.** Jacoby A et al. Gut 2005;54:1622–29; **3.** Elman S et al. Br J Dermatol 2010;162:587–93.

Differences in the PBC Worst Itch NRS questionnaire were not large enough to conclude that itch was improved

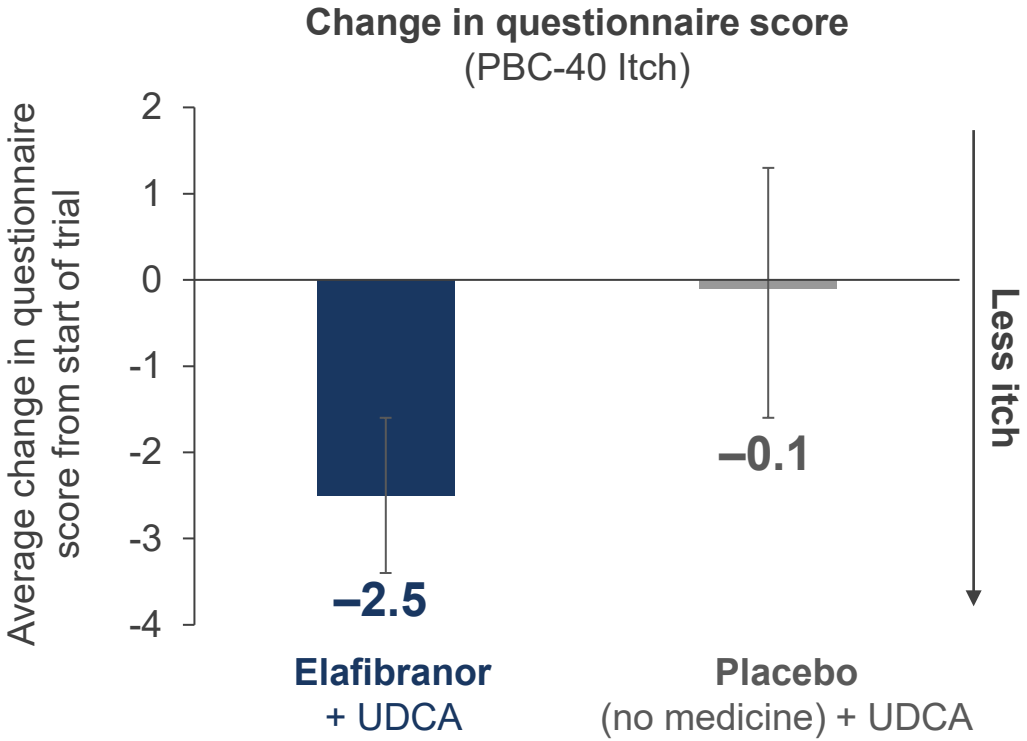


- Researchers measured how bad people's itch was using a questionnaire called PBC Worst Itch NRS
- In people with relentless itch, **according to this questionnaire, elafibranor did not reduce itch more than placebo** (the difference between the two groups was not large enough to confidently say that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

Note that a few people were unable to also take UDCA

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.

The PBC-40 questionnaire suggested that elafibranor may improve symptoms of itch after 1 year

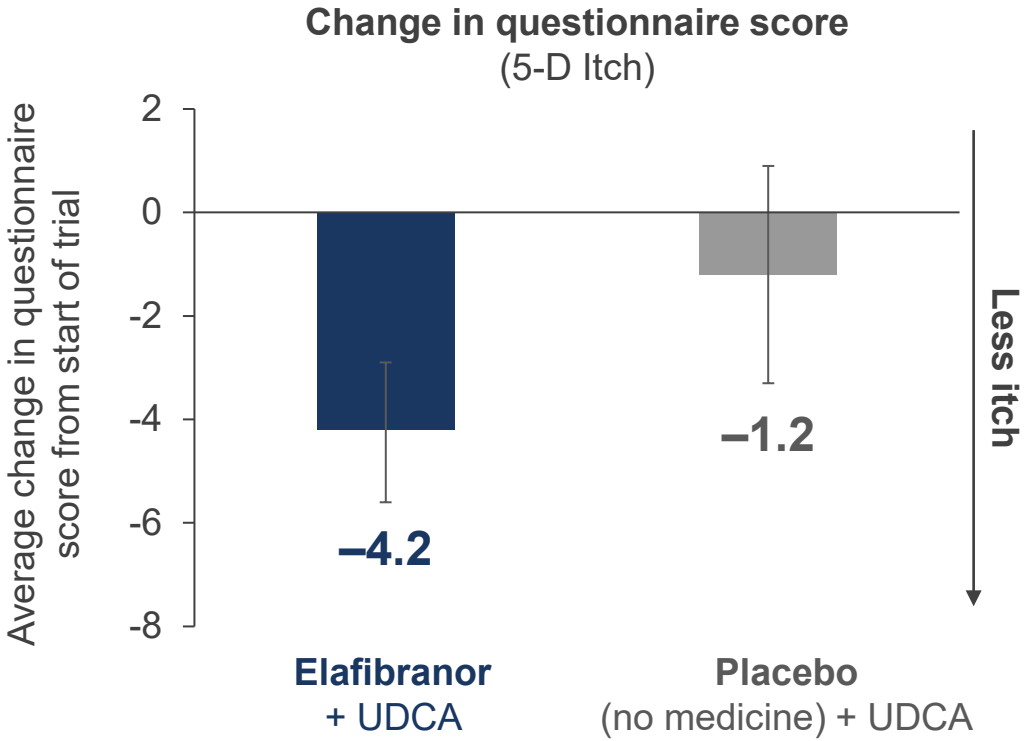


- Two other questionnaires (PBC-40 and 5-D Itch) were also used to measure itch
- In people with relentless itch, the PBC-40 questionnaire suggested that **elafibranor may improve symptoms of itch after 1 year**

Note that a few people were unable to also take UDCA

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.

The 5-D Itch questionnaire also suggested that elafibranor may improve symptoms of itch after 1 year



- In people with relentless itch, the 5-D Itch questionnaire also suggested that **elafibranor may improve symptoms of itch after 1 year**

Note that a few people were unable to also take UDCA

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.

The most common side effects of elafibranor in the trial were gut-related

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

- 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

[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.

Summary

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)

5-D: 5-Dimensional; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid.

Acknowledgments

The authors thank all patients involved in the study, as well as their caregivers, care team, investigators, and research staff in participating institutions

Acknowledgments

MEDICAL WRITING SUPPORT

- The authors thank Patrick Cox, BSc (Hons), and Oliver Palmer, BSc (Hons), of Costello Medical, London, UK for providing medical writing support, which was sponsored by Ipsen in accordance with Good Publication Practice guidelines

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

FUNDING

- The ELATIVE™ trial was funded by GENFIT S.A. and Ipsen

ELATIVE™ Principal Investigators

USA
Ana Corregidor, Victor Ankoma-Sey, Walid Ayoub, **Christopher Bowlus**, Stephen Caldwell, Hany Elbeshbeshy, Lisa Forman, Michael Galambos, Reem Ghalib, Richard Gilroy, Stuart Gordon, Ira Jacobson, Saro Khemichian, **Kris Kowdley**, Karen Krok, Marcelo Kugelmas, Sonal Kumar, **Eric Lawitz**, **Cynthia Levy**, **Marlyn Mayo**, Ashwini Mehta, Abdullah Mubarak, Andrew Muir, Anthony Post, Daniel Pratt, Mordechai Rabinovitz, Ravi Ravinuthala, Don Rockey, Peter Ruane, Mark Russo, David Sass, Andrew Scanga, **Mitchell Shiffman**, Marina Silveira, Dharmendra Verma, **John Vierling**, Kidist Yimam

Canada
Nabiha Faisal, **Mark Swain**, Catherine Vincent

Mexico
Laura Ladron De Guevara

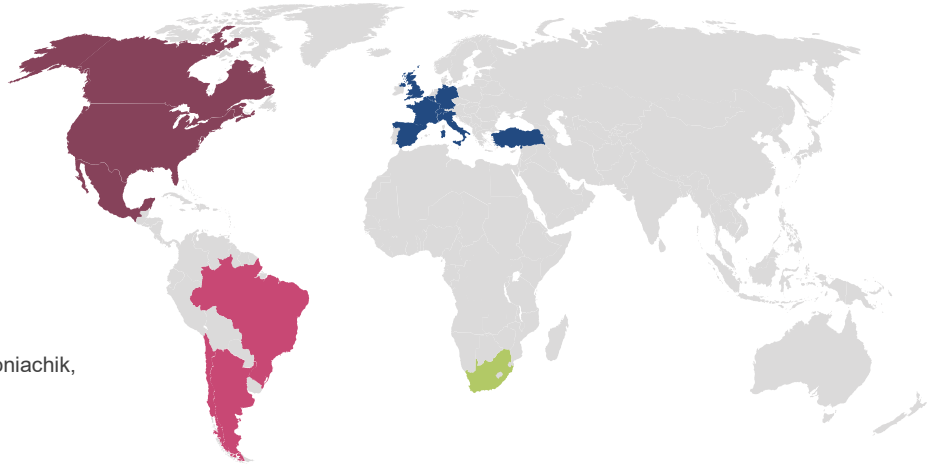
Brazil
Mario Reis Alvares-da-Silva, Eduardo Cancado

Chile
Marco Arrese, Gabriel Mezzano, Teller Jaime Poniachik, **José Miguel Valera**

Argentina
Raul Adrover, Fernando Bessone, Luis Colombato, Adrian Gadano, Omar Galdame, **Alejandra Villamil**

UK
Kuldeep Cheent, Lindsey Corless, **Michael Heneghan**, **David Jones**, Roger McCorry, George Mells, David Sheridan

France
Christophe Corpechot, Alexandra Heurgue, Marie-Noelle Hilleret, Vlad Ratziu, Philippe Sogni



South Africa
Frederik Kruger, Naayil Rajabally, Mark Sonderup

Belgium
Sven Francque, Christophe Moreno, Xavier Verhelst

Germany
Heike Bantel, Holger Hinrichsen, Wolf-Peter Hofmann, Tobias Müller, **Jörn Schattenberg**, Ingolf Schiefke, Kathrin Sprinzl

Switzerland
Susana Gomes Rodrigues, Benedetta Terziroli Beretta-Piccoli

Spain
Javier Ampuero, Jose Luis Calleja Panero, Alvaro Diaz Gonzalez, Maria Carlota Londono-Hurtado, Antonio Olveira Martin, Magdalena Salcedo Plaza, Juan Turnes, **Victor Vargas**

Italy
Pietro Andreone, Vincenza Calvaruso, **Pietro Invernizzi**, Luigi Muratori

Turkey
Ulus Akarca, Yasemin Balaban, Yusuf Yilmaz

These Principal Investigators screened at least one patient for the trial.

Full *NEJM* publication now available

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis

K.V. Kowdley, C.L. Bowlus, C. Levy, U.S. Akarca, M.R. Alvares-da-Silva, P. Andreone, M. Arrese, C. Corpechot, S.M. Francque, M.A. Heneghan, P. Invernizzi, D. Jones, F.C. Kruger, E. Lawitz, M.J. Mayo, M.L. Shiffman, M.G. Swain, J.M. Valera, V. Vargas, J.M. Vierling, A. Villamil, C. Addy, J. Dietrich, J.-M. Germain, S. Mazain, D. Rafailovic, B. Taddé, B. Miller, J. Shu, C.O. Zein, and J.M. Schattenberg, for the ELATIVE Study Investigators' Group*

*A **plain language summary** of the full paper is available in its supplementary appendix*

Full paper at:

Thank you!

Full paper