*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# Elafibranor

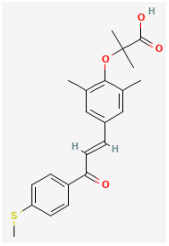
**Evidence Summary**

This dual PPAR agonist may modestly improve the metabolic profile, but the effects generally fall below the level of clinical significance in tested disease populations. It has a reasonable safety profile.

**Neuroprotective Benefit:** No studies have evaluated elafibranor for neuroprotective benefits.

**Aging and related health concerns:** Clinical studies show modest improvement to lipid profiles, glucose homeostasis, and liver function, but effects may not reach clinical significance when used as a monotherapy.

**Safety:** There was good safety and tolerability in clinical trials, with gastrointestinal events and a reversible increase in serum creatinine as the most common adverse events.

| | | |
|---|---|---|
| **Availability**: In clinical trials | **Dose**: Not established<br>Used at 80 and 120 mg/day orally in RCTs for Primary biliary cholangitis and non-alcoholic steatohepatitis | **Chemical formula:** $C_{22}H_{24}O_4S$<br>**MW**: 384.5 g/mol<br>  <br>Source: PubChem |
| **Half-life**: 34-37 hours for elafibranor, 6-9 hours for active metabolite (in adolescents) | **BBB**: Not penetrant | |
| **Clinical trials**: Tested in Phase 2 trials for dyslipidemia, insulin resistance, primary biliary cholangitis, and NASH. A Phase 3 RCT for NASH was terminated, and a Phase 3 RCT for primary biliary cholangitis is ongoing. | **Observational studies**: None | |

**What is it?**

Elafibranor, also called GFT505, is a modulator of peroxisome proliferator-activated receptor (PPAR) signaling [1]. PPARs dimerize with the retinoic acid receptor (RXR) to influence gene transcription, and play key roles in the regulation of metabolism, including glucose and lipid homeostasis. Elafibranor is a dual PPARα/PPARδ agonist. It is a biased agonist, showing more activity toward PPARα, with an $EC_{50}$ = 45 nmol/L, compared to PPARδ, with an $EC_{50}$=175 nmol/L. The active metabolite, GFT1007 shows a similar bias (PPARα $EC_{50}$=15 nmol/L, PPARδ $EC_{50}$= 75 nmol/L). Elafibranor is being developed by Genfit. It was originally under clinical development for hyperlipidemia and type 2 diabetes, but development subsequently shifted to diseases of the liver, including non-alcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH), and primary biliary cholangitis. It has received fast track designation by the FDA for NAFLD/NASH and breakthrough therapy designation for primary biliary cholangitis. Genfit has licensed elafibranor to Terns Pharmaceuticals in 2018 for development and commercialization for these indications in Greater China (Press release). In 2020, Genfit terminated its NASH Phase 3 RCT based on an interim futility analysis (Press release). In 2021, Ipsen licensed elafibranor from Genfit for worldwide development and commercialization, with the exception of the regions licensed to Tern (Press release).

**Neuroprotective Benefit:** No studies have evaluated elafibranor for neuroprotective benefits.

*Types of evidence:*

- 0 meta-analyses or systematic reviews
- 0 clinical trials
- 0 observational studies
- 0 laboratory studies

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***: None

***Human research to suggest benefits to patients with dementia***: None

***Mechanisms of action for neuroprotection identified from laboratory and clinical research***:

Elafibranor is a liver-targeted drug and is not being developed for CNS indications.

***APOE4 interactions***: N/A

**Aging and related health concerns:** Clinical studies show modest improvement to lipid profiles, glucose homeostasis, and liver function, but effects may not reach clinical significance when used as a monotherapy.

*Types of evidence:*

- 1 meta-analysis of clinicals trials for liver impairment
- 2 clinical trials for primary biliary cholangitis
- 3 clinical trials for metabolic diseases
- 2 clinical trials for NASH
- Numerous laboratory studies

**Dyslipidemia**: POTENTIAL BENEFIT

Similar to selective PPARα and PPARδ agonists, the dual PPARα/PPARδ agonist elafibranor has been shown to modify blood lipid profiles, with a primary effect on reducing circulating triglyceride levels

A meta-analysis of four trials for elafibranor in patients with liver abnormalities found that elafibranor was associated with significant reductions in total cholesterol (Mean Difference [MD] − 0.37, 95% Confidence Interval [CI] − 0.66 to − 0.08), triglycerides (MD − 0.37, 95% CI − 0.51 to − 0.24), and LDL (MD − 0.20, 95% CI− 0.33 to − 0.07) [2].

In a study of abdominally obese patients with dyslipidemia (n=94), treatment with elafibranor (80 mg/day) for 28 days reduced fasting plasma triglyceride levels (−16.7%, 95% one-sided CI −∞ to −5.3) and increased HDL-c (7.8%, 95% one-sided CI 3.0 to ∞) [3]. There were also decreases in liver enzymes (−19.9% for γ glutamyl transferase) and markers of inflammation (-11.7% for haptoglobin and -8.8% for fibrinogen). Unlike the PPARδ agonist, GW501516, elafibranor does not elicit PPAR-related gene expression changes in skeletal muscle, but rather exerts its effects by targeting the liver. Tracing studies in rodents indicated that elafibranor localizes primarily to the liver and intestine, and has low or undetectable levels in skeletal muscle [1].

**Diabetes/insulin resistance**: POTENTIAL BENEFIT

Elafibranor's impact on insulin resistance and glycemic control have been assessed in several clinical trials. While the results have primarily been positive, the effect on various metrics has been inconsistent across studies suggesting that the efficacy is modest and influenced by patient population. Despite the general beneficial effects on glucose metabolism, clinical development for elafibranor is currently focused on liver-related indications.

In abdominally obese patients with impaired glucose metabolism (n=47), the dual PPARα/PPARδ agonist elafibranor (80 mg/day) for 35 days led to a significant decrease of homeostasis model assessment of insulin resistance (HOMA-IR) (−31.4%, 95% one-sided CI −∞ to 12.5, P=0.001), fasting plasma glucose (−0.37 mmol/L, 95% one-sided CI −∞ to −0.10, P=0.01) and fructosamine (−3.6%, 95% one-sided CI −∞ to −0.20], P = 0.02), relative to placebo [3]. However, it did not significantly affect the primary outcome, the glucose tolerance test, in this study. There were also reductions in fasting plasma triglycerides (−24.8%), LDL-c (−11.0%), and the liver enzyme gamma glutamyl transferase (GGT) (−15.1%). Additionally, there were reductions in the inflammatory markers haptoglobin (-15.8%) and fibrinogen (-10%).

Elafibranor was tested in a cross-over RCT in adult males (n=22) with abdominal obesity and insulin resistance (HOMA-IR >3) [4]. The primary endpoint of this study was glucose infusion rate. Treatment at 80 mg/day for eight weeks increased the glucose infusion rate by 21%, indicative of improved peripheral insulin sensitivity, along with a 44% increase in hepatic insulin sensitivity, but did not significantly affect

fasting plasma glucose. There were reductions in fasting plasma triglycerides (relative effect size vs. placebo of −21%), LDL-c (relative effect size -13.2%), and apolipoprotein B (relative effect size −14%), as well as an increase in apolipoprotein A-II (relative effect size +11.8%). Additionally, there were reductions in liver enzymes (GGT: −30.4% and alanine aminotransferase [ALT]: −20.5%).

**Nonalcoholic Steatohepatitis**: NO CLINICALLY SIGNIFICANT BENEFIT

Elafibranor was in clinical development for NAFLD/NASH, however, its Phase 3 RCT RESOLVE-IT (NCT02704403) (n=717 active and n=353 placebo) was terminated in 2020 based on an interim futility analysis for its primary endpoint of achieving resolution of NASH without worsening of fibrosis relative to placebo (Press release). In this trial, elafibranor was being tested at a dose of 120 mg/day for 72 weeks. The primary endpoint response rate was 19.2% among those treated with elafibranor compared with 14.7% in the placebo group (*P* =.0659) (MPR). Additionally, there was no significant difference in the number of patients treated with elafibranor who achieved fibrosis improvement of at least one stage (24.5% vs 22.4% placebo), and no significant differences in metabolic parameters. A Phase 2 RCT (NCT03953456) examining the effect of 120 mg elafibranor for six weeks on hepatic liver composition in patients with NAFLD was terminated in 2020. A Phase 2 RCT (NCT03883607) examining 80 or 120 mg elafibranor for three months in adolescents with NASH was also terminated. The lack of significant benefit in the Phase 3 RCT is not particularly unexpected based on the results from the Phase 2 study and general lack of translatability for current NASH preclinical models. Elafibranor has generally been considered to be insufficient as a monotherapy for NAFLD/NASH, but may offer benefit as part of a combination therapy [1]. It is unclear whether Genfit will continue clinical development as part of a combination therapy. Genfit appears to be pivoting toward the orphan condition Acute on chronic liver failure (ACLF), which is acute deterioration of preexisting chronic liver disease (Corporate presentation).

Elafibranor (80 or 120 mg) was tested in a Phase 2 RCT GOLDEN-505 (NCT01694849) in 274 patients with NASH for one year [5]. Although there was no significant difference on the primary outcome of NASH resolution using the protocol definitions, there was a change in the recommendation for the definition of NASH resolution during the course of the trial. When the results were re-analyzed post-hoc using the revised definition, NASH resolved without fibrosis worsening in a higher proportion of patients in the 120-mg elafibranor group vs the placebo group (19% vs 12%; Odds Ratio [OR]: 2.31; 95% CI 1.02 to 5.24; P = 0.045). Additionally, in subgroup analysis, in patients with NAFLD activity score ≥4 (n = 234) there was a higher percentage reaching NASH resolution without fibrosis in the 120-mg elafibranor group relative to placebo based on both protocol (20% vs 11%; OR: 3.16; 95% CI 1.22 to 8.13; P = 0.018) and revised (19% vs 9%; OR: 3.52; 95% CI 1.32 to 9.40; P = 0.013) definitions. Patients in the 120-mg elafibranor group also showed significant reductions in liver enzymes (ALT, GGT, and alkaline

phosphatase), lipids (triglycerides, LDL-c), glucose profiles (fasting serum glucose, HbA1c, insulin, HOMA-IR), and inflammatory markers (high-sensitivity C-reactive protein, fibrinogen, and haptoglobin). Additionally, there were significant reductions in serum panel biomarkers of steatosis and fibrosis, including the SteatoTest, Fatty Liver Index, Fibrotest/FibroSure, and the NAFLD Fibrosis score.

A meta-analysis of four trials for elafibranor in patients with liver abnormalities found that elalfibranor use was associated with significant reductions in the liver enzymes ALT (Mean Difference [MD] − 4.60 95% CI, − 8.17 to − 1.04), GGT (MD − 16.57, 95% CI − 26.59 to − 6.56), and alkaline phosphatase (MD − 14.4, 95% CI − 18.99 to − 9.91) [2].

**Primary biliary cholangitis**: POTENTIAL BENEFIT

Primary biliary cholangitis (PBC) is a chronic disease involving the degeneration of the bile ducts in the liver. It involves liver inflammation, and may be a type of autoimmune condition. It primarily affects women. Elafibranor is currently under clinical development as a second-line therapeutic for PBC.

In a Phase 2 placebo-controlled RCT (NCT03124108), patients with PBC were treated with

80 mg or 120 mg of the dual PPARα/ PPARδ agonist elafibranor for 12 weeks [6]. On the primary endpoint, relative change in alkaline phosphatase, there was a +3.2±14.8% increase in the placebo group, -48.3±14.8% decrease in the elafibranor 80 mg group, and -40.6±17.4% decrease in the elafibranor 120 mg group. There was also a reduction in itching symptoms, and significant reductions in inflammatory markers, including IgM, C-reactive protein, and haptoglobin, relative to the placebo-treated group. In an RCT testing elafibranor in patients with cholestatic disease (PBC, PSC or SSC) with moderate to severe pruritus (n=38 active, n=36 placebo) for 21 days, 45% of elafibranor patients had reduced (≥50%) pruritus compared to 11% in the placebo group [7]. Alkaline phosphatase was also significantly reduced (35% vs 6%). A Phase 3 RCT (NCT04526665) is currently underway evaluating the effect of 80 mg elafibranor on cholestasis.

**Safety:** There was good safety and tolerability in clinical trials, with gastrointestinal events and a reversible increase in serum creatinine as the most common adverse events.

*Types of evidence:*

- 6 clinical trials
- Numerous laboratory studies

The pharmacokinetics and pharmacodynamics of elafibranor were studied in several populations in Phase 1 studies, however, the results of those studies are largely unavailable. In a cohort of adolescents (age 8 to 17) with NASH (n=10) (NCT03883607) dosed at 80 or 120 mg/day, liver enzymes (AST, ALT, GGT, ALP) generally decreased in the 120 mg group. The terminal half-life of elafibranor at 80 mg was 34.170 hours, and at 120 mg it was 37.620 hours. The terminal half-life of the active metabolite, GFT1007 was 9.572 ± 5.592 hours at 80 mg and 6.682 ± 1.120 hours at 120 mg. There were no severe adverse events, and all laboratory and hematological parameters were normal.

In obese participants with dyslipidemia or impaired glucose metabolism, treatment with 80 mg/day of the dual PPARα/PPARδ agonist elafibranor for approximately one month, did not result in specific adverse safety signals [3]. Possible treatment-related events included mild gastrointestinal events. A slight, reversible increase in creatinine was seen in some patients, consistent with other PPARα agonists. All other laboratory test parameters were normal. Changes to lipid parameters reversed within two weeks of drug cessation. Treatment in a similar population for eight weeks was associated with a similar safety profile, with a greater proportion of placebo participants reporting adverse events relative to the active drug group [4].

In NASH patients, clinical adverse events were generally mild and similar across placebo and treatment groups (80 and 120 mg/day) [5]. A mild, reversible increase in serum creatinine occurred with elafibranor (4.31 ± 1.19 µmol/L). There were six reported neoplastic serious adverse events, but only one was in the elafibranor group, and it is unlikely drug-related. The safety and tolerability of elafibranor in the terminated Phase 3 RESOLVE-IT RCT were reported to be similar to prior trials (Press release). Treatment-emergent and treatment-related adverse events and severe adverse events were balanced across the treatment arms (AASLD 2020).

In patients with primary biliary cholangitis, treatment-emergent adverse events were balanced across groups, and non-serious events were mild or moderate [6]. Two patients in the 120 mg elafibranor group experienced severe adverse events (ischemic stroke and 3X elevation of aminotransferase activity).

***Drug interactions***: Indomethacin inhibits the enzyme responsible for the transformation of elafibranor into GFT1007 *in vitro*. A clinical trial (NCT03985969) was conducted to assess the effect of indomethacin on the pharmacokinetics of elafibranor, but the results are not publicly available. Other interactions have not been disclosed, but due to its mechanism of action, it may interact with other PPAR agonists and metabolic modulators, such as anti-diabetic drugs. Since it is biased toward PPARα agonism, it may have similar interactions, as the preferential PPARα agonist, fenofibrate (Drugs.com).

**Sources and dosing:**

Elafibranor is not currently approved for any condition. It is in Phase 3 clinical trials for primary biliary cholangitis by Genfit. It has been tested at 80 mg/day for primary biliary cholangitis and 120 mg/day for NASH. Elafibranor is currently licensed by Tern Pharmaceuticals for the Greater China region and to Ipsen for the rest of the world market.

**Research underway:**

According to Clinicaltrials.gov, there is one active clinical trial for elafibranor. It is being tested in a Phase 3 RCT (ELATIVE) (NCT04526665) in patients with primary biliary cholangitis. The estimated primary study completion date is in 2023, while the estimated study completion date is in 2028.

**Search terms:**

Pubmed, Google: Elafibranor, GFT505

- Cardiovasular, Diabetes, Metabolic syndrome, NASH, clinical trial, safety

Websites visited for Elafibranor:

- Clinicaltrials.gov
- PubChem
- DrugBank.ca
- Cafepharma

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