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

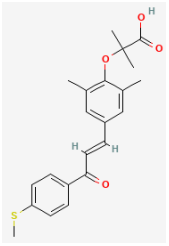
Evidence Summary

This dual PPARα/δ agonist shows benefit in a rare liver disease, but metabolic benefits are not clinically meaningful in other populations. Safety is reasonable, but there is a risk for muscle injury when used in combination with statins.

Neuroprotective Benefit: Elafibranor is a liver-targeted drug and has not been tested for neuroprotective properties.

Aging and related health concerns: Clinical studies show modest improvement to lipid profiles, glucose homeostasis, and liver function, but aside from rare forms of cholangitis, these effects have not reached clinical significance when used as a monotherapy.

Safety: Gastrointestinal events were the most common in clinical trials, though cases of muscle and liver injury were also reported, as well as elevations in serum creatinine and creatine phosphokinase. Long term safety still needs to be established.

Availability: Rx	**Dose**: The recommended dose for primary biliary cholangitis is 80 mg/day, orally.	**Chemical formula:** $C_{22}H_{24}O_4S$ **MW**: 384.5 g/mol  Source: PubChem
Half-life: 70.2 hours for elafibranor, 15.4 hours for active metabolite (GFT1007)	**BBB**: Not penetrant	
Clinical trials: It has been tested in Phase 2 and Phase 3 (n=161) RCTs in primary biliary cholangitis, as well as Phase 2 trials for dyslipidemia, insulin resistance, and NASH. A Phase 3 RCT for NASH was terminated. A Phase 2 RCT in primary sclerosing cholangitis is ongoing, as are additional Phase 3 trials in primary biliary cholangitis.	**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).

In June 2024, elafibranor was granted accelerated approval by the FDA as the first-in-class dual PPAR α/PPARδ agonist for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA (Press release). Elafibranor was also given conditional marketing authorization by the EMA in September 2024. Elafibranor is marketed under the brand name Iqirvo® by Ipsen. It was in development by Genfit, but was licensed to Ipsen in 2021 for development, manufacturing, and commercialization. The exception to this worldwide license is the Greater China region (China, Taiwan, Hong Kong, and Macau), as Genfit had previously licensed elafibranor for development in this region to Terns Pharmaceuticals in 2018 (Press release).

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 received fast track designation by the

FDA for NAFLD/NASH and breakthrough therapy designation for primary biliary cholangitis, but in 2020, Genfit terminated its development in NASH based on an interim futility analysis of a Phase 3 trial (Press release).

Neuroprotective Benefit: Elafibranor is a liver-targeted drug and has not been tested for neuroprotective properties.

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 aside from rare forms of cholangitis, these effects have not reached clinical significance when used as a monotherapy.

Types of evidence:

- 1 meta-analysis of clinicals trials for liver impairment
- 3 clinical trials for primary biliary cholangitis
- 3 clinical trials for metabolic diseases

- 3 clinical trials for NASH
- 1 clinical trial for primary sclerosing cholangitis
- Numerous laboratory studies

Dyslipidemia: POTENTIAL MODEST 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-cholesterol (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). In the Phase 3 ELATIVE trial in patients with primary biliary cholangitis (n=161), elafibranor treated patients experienced sustained reductions in levels of total cholesterol, LDL-c, VLDL-c, and triglycerides, while HDL-c levels were stable [4].

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 MODEST 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 γ 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) [5]. 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, the 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 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 1 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. An open-label Phase 2 RCT (NCT03883607) examining 80 or 120 mg elafibranor for three months in ten adolescent males (mean age 15.1) with NASH was also terminated prematurely due to the failure of the Phase 3 RESOLVE-IT trial in adult NASH [7]. Participants were treated with elafibranor at a dose of 80 mg or 120 mg per day for 12 weeks. Treatment at the 120 mg dose led to a decrease in levels of the liver enzyme ALT (87 U/L to 52 U/L; -37.4% SD 23.8%). However, the 80 mg dose did not reduce ALT levels (82 U/L to 100 U/L; +18% SD 57).
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 there will be clinical efforts to use elafibranor as part of a combination therapy.

Elafibranor (80 or 120 mg) was tested in a Phase 2 RCT GOLDEN-505 (NCT01694849) in 274 patients with NASH for one year [6]. 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 nonalcoholic fatty liver disease 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 elafibranor 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].

Alcohol-associated liver disease: POTENTIAL BENEFIT (Preclinical)
A preclinical study in mice found that elafibranor attenuated hepatic steatosis, apoptosis, and fibrosis in a model of alcohol-associated liver disease (EtOH + CCl_4-induced) [8]. These effects likely stemmed from elafibranor-mediated promotion of lipolysis, beta-oxidation, and autophagy. Treatment with elafibranor also protected the integrity of the intestinal barrier and preserved autophagy in the intestine, in this model.
The translatability of these findings is unclear, particularly considering the lack of clinical efficacy in NASH, despite evidence for protective effects in preclinical models.

Primary biliary cholangitis: BENEFIT
Primary biliary cholangitis (PBC) is a chronic disease involving the degeneration of the bile ducts in the liver. It involves liver inflammation, may be a type of autoimmune condition, and primarily affects women. Elafibranor was recently approved as a second-line treatment for PBC in patients with an

inadequate response or intolerance to the first line therapy, UDCA, based on the results of the randomized, double-blind, placebo-controlled Phase 3 ELATIVE trial.
A greater percentage of participants treated with elafibranor achieved the primary outcome of a biochemical response, defined as an alkaline phosphatase level of <1.67 times the upper limit of the normal (ULN) range, with a reduction of ≥15% from baseline, and normal total bilirubin levels at week 52 (51% vs 4%) in the Phase 3 trial [4]. ELATIVE (NCT04526665) included 161 patients with PBC randomized two to one to 80 mg/day oral elafibranor or placebo for 52 weeks. Responses occurred within four weeks and were maintained through the duration of the study. A greater percentage of elafibranor-treated patients also achieved alkaline phosphatase normalization (15% vs 0%). Pruritus (itch), which is a common symptom of PBC, was not significantly reduced with elafibranor in participants with moderate to severe pruritus (n=66), based on the Worst Itch Numeric Rating Scale (WI-NRS) (-1.93 vs -1.15, on a ten-point scale). But, unlike other PBC medications, such as obeticholic acid, elafibranor did not exacerbate itch. Participants in this study are continuing to be followed for up to an additional 52 weeks and will have the option to enter an open label extension out to five years.

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 [9]. On the primary endpoint, of 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 [10]. Alkaline phosphatase levels were also significantly reduced (35% vs 6%).

Elafibranor was granted accelerated approval, based on a surrogate endpoint, the biochemical response. Therefore, additional confirmatory trials are needed to provide evidence for a meaningful clinical benefit in this population. Several of these trials are ongoing, including the Phase 3 ELSPIRE RCT (NCT06383403), which is similar to the ELATIVE trial, the Phase 3 ELFIDENCE RCT (NCT06016842) assessing long-term safety and efficacy, and the open-label Phase 4 ELFINITY study (NCT06447168) assessing safety, tolerability, and efficacy in a real-world setting.

Primary sclerosing cholangitis: POTENTIAL BENEFIT

Primary sclerosing cholangitis is a disease of the bile ducts which can eventually lead to liver failure [11]. Inflammation leads to the scarring of the bile ducts, blocking the flow of digestive bile from the liver to the small intestine. It commonly occurs in conjunction with inflammatory bowel disease, and occurs more often in men. Similar to PBC, the first line treatment is UDCA, which manages symptoms but does not alter the course of disease progression.

Elafibranor was tested at doses of 80 mg and 120 mg/day in the randomized, double-blind, placebo-controlled Phase 2 ELMWOOD trial in 68 patients with primary sclerosing cholangitis (NCT05627362). To date, only topline data has been reported (Press release). There were dose-dependent reductions in alkaline phosphatase with both the 80 mg (-103.2 U/L) and 120 mg (-171.1 U/L) doses, relative to placebo (+32.1 U/L) at week 12. Reductions were also observed on other disease-relevant liver enzymes, including ALT and GGT.

Safety: Gastrointestinal events were the most common in clinical trials, though cases of muscle and liver injury were also reported, as well as elevations in serum creatinine and creatine phosphokinase. Long term safety still needs to be established.

Types of evidence:

- 8 clinical trials
- Numerous laboratory studies

The most common adverse events associated with elafibranor are gastrointestinal related. In the Phase 3 ELATIVE RCT in patients with primary biliary cholangitis (n=161), the most common (>10%) adverse events occurring more frequently with elafibranor were abdominal pain (11%), diarrhea (11%), nausea (11%), and vomiting (11%) [4]. Elevated creatine phosphokinase levels were more common with elafibranor, with four elafibranor-treated participants discontinuing the study due to creatine phosphokinase >5 times the ULN with or without associated symptoms, or >3 times the ULN in the presence of associated symptoms. Notably, two of these cases occurred with concomitant statin use, while a serious case of rhabdomyolysis occurred in another elafibranor-treated participant taking statins. One case of potential drug-induced liver injury, as defined by aminotransferases >3 times the baseline value if baseline was elevated or >3 times or 5 times the ULN if the baseline value was normal, or bilirubin >2 times the ULN, or both, occurred with elafibranor, along with two cases in the placebo group. The case with elafibranor was adjudicated as possible drug-induced liver injury, while those in the

placebo group were adjudicated as probable drug-induced liver injury. Elevations in serum creatinine (>25% above baseline) were more common with elafibranor (10.2% vs 7.5%), and there were more cases of acute kidney injury with elafibranor relative to placebo (3 vs 1).
In the Phase 2 trial in this population, 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).

The FDA prescribing label indicates that the most common adverse events (≥5%) associated with elafibranor in clinical trials were weight gain, diarrhea, abdominal pain, nausea, vomiting, arthralgia, constipation, muscle injury, fracture, gastroesophageal reflux disease, dry mouth, weight loss, and rash. The label contains warnings for myalgia (muscle pain), myopathy, and rhabdomyolysis, increased fracture risk, fetal harm, drug-induced liver injury, and hypersensitivity. Elafibranor should not be used in patients with biliary obstruction.

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 [5].
In NASH patients, clinical adverse events were generally mild and similar across placebo and treatment groups (80 and 120 mg/day) [6]. 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).

Elafibranor was generally well-tolerated in patients with primary sclerosing cholangitis in the Phase 2 ELMWOOD trial, with a similar incidence of adverse events for the 80 mg dose (68.2%) and placebo groups (69.6%), and a higher incidence at the 120 mg dose (78.3%), based on reported study highlights (Press release). There were no serious adverse events in participants treated with elafibranor.

A preclinical study in a mouse model of NASH (choline-deficient high-fat diet) found that elafibranor treatment increased levels of S100A4 in the liver [12]. S1004A promotes the epithelial-mesenchymal transition (EMT), a process that makes cells more migratory and invasive, and is associated with tumorigenesis. The effect was found to be related to the activation of PPARδ. This is notable because PPARδ has been implicated in cancer, though effects appear to be context dependent. This suggests that additional monitoring for cancer may be warranted while taking elafibranor.

Drug interactions: According to Drugs.com, there are 244 drug interactions with elafibranor, 15 of which are major interactions. The FDA prescribing label indicates that elafibranor has interactions with hormonal contraception, such that non-hormonal contraceptive methods should be used for at least three weeks after the last dose. Monitoring for muscle injury is needed when used with HMG-CoA reductase inhibitors (statins), and monitoring of the biochemical liver response is needed when used with rifampin (an antibiotic). Elafibranor should be administered at least four hours before or after taking bile acid sequestrants.

Sources and dosing:

Elafibranor is approved for the treatment of primary biliary cholangitis in adult patients in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. The recommended dose is 80 mg/day, orally, with or without food. It is marketed under the brand name Iqirvo® by Ipsen.

Research underway:

According to Clinicaltrials.gov, there are currently six active clinical trials testing elafibranor, three are actively recruiting, while three are active but no longer recruiting.

The open-label Phase 3 ELONSEN trial is testing elafibranor in adult Japanese participants with primary biliary cholangitis (NCT06730061). The study has a primary completion date in 2026 and a study completion date in 2032.

ELFIDENCE is a Phase 3 randomized, parallel-group, double-blind, placebo-controlled, study on the long-term safety and efficacy of elafibranor (80 mg) in adults with primary biliary cholangitis (NCT06016842). The study has an expected completion date in 2029.

ELFINITY is a prospective non-interventional, Phase 4 observational study of the efficacy, safety, and tolerability of elafibranor (80 mg) in adults with primary biliary cholangitis in a real-world setting (NCT06447168). The study has an expected completion date in 2032.

The Phase 3 ELATIVE trial in patients with primary biliary cholangitis (NCT04526665) had a primary completion date in 2023 and has a study completion date in 2028.

ELSPIRE is a Phase 3 randomized, parallel-group, double-blind, placebo-controlled, study to evaluate the effect of elafibranor (80 mg) on the normalization of alkaline phosphatase in adult participants with primary biliary cholangitis and inadequate response or intolerance to ursodeoxycholic acid (NCT06383403). The study has an expected completion date in 2026.

ELMWOOD is a Phase 2 double-blind, randomized, placebo-controlled study and open label long term extension to evaluate the safety and efficacy of elafibranor in adult participants with primary sclerosing cholangitis (NCT05627362). The trial has an expected completion date in 2026.

Preclinical research

Additionally, there are other research groups working on developing novel dual PPARα/δ agonists, including those with sub-nanomolar potency [13; 14].

Search terms: Elafibranor, GFT505

Pubmed, Google:

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

Websites visited for Elafibranor:

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

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