*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.*

# EC5026

**Evidence Summary**

EC5026 is an sEH inhibitor that should promote levels of anti-inflammatory EETs. However, clinical evidence is lacking, and the risk of pro-oncogenic activities needs to be investigated.

**Neuroprotective Benefit:** EC5026 may increase levels of anti-inflammatory signaling molecules and shows some benefit in preclinical models. However, the signaling pathways are complex and the utility of sEH inhibitors in humans is unclear.

**Aging and related health concerns:** EC5026 is thought to have cardioprotective and anti-inflammatory actions, and there is some benefit in preclinical models. However, the utility of inhibiting sEH in humans is unclear.

**Safety:** EC5026 is reported to be very selective for its target and an initial clinical trial found no safety concerns. Still, there is no data in large groups of subjects and/or long-term use of EC5026, and the risk of cancer must be assessed.

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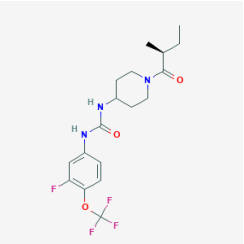
|---|---|---|
| **Availability**: in clinical development | **Dose**: The single completed trial enrolled 40 subjects. | **Chemical formula:** $C_{18}H_{23}F_4N_3O_3$ **MW**: 405.4  Source: PubChem |
| **Half-life**: 42 – 59 hours | **BBB**: Not available | |
| **Clinical trials**: The single completed trial enrolled 40 subjects. | **Observational studies**: None | |

**What is it?**

Arachidonic acid (AA) is an omega-6 polyunsaturated fatty acid that plays critical roles in maintaining cellular membrane fluidity and function (Tallima & El Ridi, 2018). As reviewed in Wang et al., 2021, the metabolism of arachidonic acid, known as the arachidonic pathway, is a very complex and wide-ranging signaling pathway that produces many different biologically active lipid-based signaling molecules. The AA pathway has three different branches: the COX pathway metabolized by cyclooxygenases (COXs); the LOX pathway mediated by lipoxygenases (LOXs); and the cytochrome p450 (CYP) pathway, metabolized by CYP enzymes omega-hydrolases and epoxygenases. All three of these pathways play roles in inflammation and immune signaling; for instance, NSAIDs like ibuprofen function by inhibiting certain COX enzymes. The CYP pathway can produce, among other arachidonic acid metabolites, a class of epoxy fatty acids called epoxyeicosatrienoic acids (EETs). EETs have a dizzying array of potential activities, including vasodilation and roles in cellular proliferation, differentiation, and migration. EETs also have a variety of anti-inflammatory actions, including through reduction of NF-κB signaling. There are some reports that EETs may modulate aspects of mitochondrial dysfunction and/or ER stress (reviewed by Inceoglu et al., 2017).

EETs are rapidly metabolized by an enzyme called soluble epoxide hydrolase (sEH) to the corresponding diol or dihydroxyeicosatrienoic acid (DHET); these metabolites are typically less active if not fully inactive. Inhibiting sEHs is therefore one method by which you can potentially increase EET levels and their desired activities.

EC5026 is an oral sEH inhibitor developed by EicOsis that inhibits sEH at picomolar concentrations. It is currently in trials for neuropathic pain. One Phase 1a study has been completed in healthy volunteers, and the company is planning future Phase 1 trials, including in patients with pain (EicOsis Company Website).

**Neuroprotective Benefit:** EC5026 may increase levels of anti-inflammatory signaling molecules and shows some benefit in preclinical models. However, the signaling pathways are complex and the utility of inhibiting sEH inhibitors in humans is unclear.

*Types of evidence:*

- 1 review
- 8 laboratory studies

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***:

No human studies have assessed the impact of EC5026 or other soluble epoxide hydrolase inhibitors on prevention of dementia, decline, or improved cognitive function.

***Human research to suggest benefits to patients with dementia***:

No human studies have assessed the impact of EC5026 or other soluble epoxide hydrolase inhibitors in patients with dementia.

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

There are a few pieces of observational or epidemiological data that indicate that inhibition of sEH (and potential concomitant increase in EET levels) may be neuroprotective. Four papers reported increased sEH in postmortem brain tissue of AD patients (Lee et al, 2019, Ebright et al., 2022, Griñán-Ferré et al 2020, Ghosh et al., 2020). When two of these groups looked at EET levels, one found decreased EET levels in a mouse model of AD, whereas the other group found increased levels of EET in postmortem brain tissue from AD patients (Ghosh et al., 2020; Ebright et al., 2022). Single nucleotide polymorphisms (SNPs) that reduce activity of an enzyme that generates EETs has been associated with sporadic AD in certain populations. SNPs that reduce the function of sEH may be protective in stroke, with preclinical models indicating this may be through increasing the levels of EETs, though there is controversy in the literature as to the true effects of altered function of sEH, with some large population studies finding no association between SNPs of sEH and stroke (reviewed briefly by Kodani & Morisseau, 2019).

Inflammatory cells and molecules can be an important part of recovery from injury, but resolution of this inflammation is also often necessary. EETs are thought to be pro-resolving, including through reduction of NF-κB. Some studies indicate that EETs shift microglia towards anti-inflammatory phenotypes; studies of sEH inhibitors find decreases in inflammatory cytokines and increases in anti-inflammatory cytokines. Some anti-inflammatory actions and benefits of sEH modulation have been seen in models of stroke, brain hemorrhage, seizure, and traumatic brain injury. The vasodilatory

properties of EETs may also play a neuroprotective role in stroke. EETs may also lead to increases in BDNF (Kodani & Morisseau, 2019).

sEH gene ablation was studied in the context of genetic AD mouse models. The authors found that sEH levels were increased in the AD mouse model compared to wild-type mice. The researchers then assessed a mouse line that had AD mutations and no gene for sEH. They found that the deletion of the sEH gene led to improved nesting behavior and some measures of spatial learning and memory, as well as decreased Aβ deposition in the brain as compared to AD mice with sEH. Curiously, the authors also found that sEH depletion in the AD mice increased astrogliosis, but also increased the production of anti-inflammatory cytokines IL-4 and IL-10 as compared to AD mice with sEH (Lee et al, 2019).

Another study assessed pharmacological inhibition of sEH in AD animal models. This paper also reported increased sEH in postmortem AD brain compared to healthy controls, and in mouse models of AD compared to wildtype. They treated different AD animal models with three different sEH inhibitors. They found that compared to vehicle-treated mice, mice treated with sEH inhibitors had decreased levels of pro-inflammatory cytokines like TNF-α. They also reported that sEH treatment reduced Aβ plaque burden and levels of phosphorylated tau as compared to vehicle treatment, and that mice treated with sEH inhibitors had improved cognitive performance as measured by short-term and long-term assessment of novel objects (Griñán-Ferré et al 2020).

sEH modulation has also been evaluated in pharmacological Parkinson's disease (PD) models. Researchers found that sEH inhibitors or gene deletion protected against neuronal loss and improved measures of dopamine transmission as compared to vehicle treatment. The researchers found that levels of sEH in PD relevant brain regions increased in pharmacological models of PD as compared to control, and that levels of sEH were also higher in brain tissue samples from patients with dementia with Lewy bodies (DLB) (Ren et al., 2018).

***APOE4 interactions***:

As APOE4 is involved in lipid regulation and E5026 modulates lipid-based signaling pathways, there is potential for interactions with APOE4 genotype. However, neither EC5026 nor other sEH inhibitors have been assessed for differential effects in APOE4 carriers.

**Aging and related health concerns:** EC5026 is thought to have cardioprotective and anti-inflammatory actions, and there is some benefit in preclinical models. However, the utility of inhibiting sEH in humans is unclear.

*Types of evidence:*

- 1 randomized controlled trial

- 1 observational study
- 1 review
- 3 laboratory studies

**Neuropathic Pain:** PENDING RESULTS, POTENTIAL FOR BENEFIT

As reviewed in Hammock et al, 2021, preclinical studies with EC5026 have indicated potential use of this drug for a variety of pain conditions, including neuropathic pain, pain from chemotherapy, and postsurgical pain. Another sEH inhibitor, *t*-TUCB, has been used to treat pain in small groups of companion animals, such as laminitis in horses, and osteoarthritic pain in dogs.

EC5026 has been tested in one single ascending dose Phase 1 trial with 40 healthy volunteers, testing doses from 0.5 mg to 24 mg. An 8 mg dose is being tested in a second Phase I trial in 18 healthy subjects. Both of these trials assessed safety and pharmacokinetics of EC5026, with the ultimate goal of treating patients with pain. The second trial is also examining food effects.

EC5026 has not been used in humans for other indications. However, other sEH inhibitors have been tested in clinical trials. Brief summaries of relevant results are included below. These results may not reflect how EC5026 would act in the clinic but could be edifying given the lack of human data with EC5026.

**Stroke:** POTENTIAL FOR BENEFIT

Preclinical models and some observational studies indicate potential benefit for inhibition of sEH in stroke. GSK2256294, an sEH inhibitor, was tested in a 10-day randomized, double-blind, placebo-controlled trial of 19 patients with aneurysmal subarachnoid hemorrhage. In the GSK2256294 group the authors found an increase in serum EET levels, increase in EET/DHET ratio in serum, and trend towards decrease in CSF inflammatory cytokines, though GSK2256294 is not blood-brain barrier penetrant and they did not observe increases in EET concentrations in CSF. The patients in the treatment group also had improvements in clinical outcome such as shorter ICU and hospital stay, but this may have been due to less severe initial neurological injury (Martini et al., 2022).

**Insulin Sensitivity:** NO KNOWN BENEFIT

In preclinical models of diabetes and insulin resistance, inhibition or depletion of sEH improves insulin sensitivity. In humans, loss-of-function variants of the gene that codes for sEH are associated with increased insulin sensitivity in the context of obesity and decreased vascular resistance. An sEH inhibitor GSK2256294 was tested in 16 patients with obesity and prediabetes. This study was randomized, double-blinded, and placebo controlled. The inhibitor did indeed reduce sEH activity and also levels of

F2-isoprostanes, a biomarker of oxidative stress, but there were no changes in insulin sensitivity or levels of EETs in circulation or in muscle tissue. (Luther et al., 2021).

**Blood Pressure and Kidney Function**: THEORETICAL BUT NO PROVEN BENEFIT

As reviewed in Wang et al., 2021 and Imig & Hammock, 2009, animal studies indicate that EETs can have vasodilatory and/or anti-hypertensive effects. EETs appear to mediate blood pressure through modulation of both vascular resistance and sodium excretion from the kidneys. In preclinical studies, AUDA, an sEH inhibitor, lowered blood pressure in angiotensin models of hypertension and also protected against acute nephrotoxicity.

However, the study from Luther and colleagues of GSK2256294 in 16 patients with obesity and diabetes found no changes in blood pressure with this inhibitor of sEH (Luther et al., 2021).

**Cardiovascular Disease:** THEORETICAL BENFIT

Preclinical work indicates a variety of potential benefits mediated by EETs, whether by increasing the production, direct administration, or by decreasing the degradation through sEH inhibitors (reviewed in Wang et al., 2021). Modulation of EETs in preclinical work can be cardioprotective in models of both ischemic and non-ischemic cardiomyopathies and can have benefits in conditions ranging from heart failure to cardiac arrhythmias to atherosclerosis. Polymorphisms in genes that lead to lower production of EETs have been seen to be more prevalent in patients with coronary artery disease than in healthy controls. EETs may also play roles in angiogenesis.

**Cancer** THEORETICAL HARM

Modulation of EET levels through genetic manipulation, exogenous EET administration, and sEH inhibition all promoted tumor growth and metastasis (Panigrahy et al., 2012). Deletion of sEH increased primary tumor growth in a genetic mouse model of cancer (Kesavan et al., 2021).

As reviewed by Wang et al., 2021, EETs can promote cellular proliferation, migration, and angiogenesis, and therefore may play a role in cancer. Genes that code for EET-producing enzymes are upregulated or altered in several cancers. While the anti-inflammatory actions of EETs may provide some counterbalance to the pro-oncogenic activities, this is a safety area that requires careful attention and as of yet has not been rigorously explored in humans.

**Safety:** EC5026 is reported to be very selective for its target and an initial clinical trial found no safety concerns. Still, there is no data in large groups of subjects and/or long-term use of EC5026, and the risk of cancer must be assessed.

*Types of evidence:*

- 2 randomized controlled trials
- 1 editorial
- 5 reviews

The safety profile of EC5026 is relatively unknown. EC5026 has been tested in one Phase 1a single ascending dose study in 40 healthy volunteers. The study tested doses ranging from 0.5 mg to 24 mg. EicOsis reported that the drug was well-tolerated with no drug-related safety concerns or adverse events (Hammock et al., 2021). There is a second ongoing Phase I trial of EC5026, but results are not yet available (NCT04908995).

Studies of other sEH inhibitors may offer some insight into potential side effects of this class of medication.

GSK2256294 is an sEH inhibitor that has been tested for multiple indications. An early study of pharmacokinetics, pharmacodynamics, and safety of GSK2256294 in 82 subjects – some healthy volunteers, others who were smokers and had obesity – found no serious adverse events that were attributed to the drug. The most frequent adverse event was headache, though this was similar in incidence between the treatment group and placebo (Lazaar et al., 2016). In a randomized, double-blind, placebo-controlled trial of GSK2256294 in 16 patients with obesity and prediabetes, the researchers reported that GSK2256294 was well-tolerated with no laboratory adverse events and no effect of the drug on electrolyte levels, kidney function, or ECG QT interval. There were few adverse events and given the size of the trial, no large differences were seen between groups (Luther et al., 2021). A study of GSK2256294 in patients with aneurysmal subarachnoid hemorrhage found that GSK2256294 was similarly well-tolerated, with no serious adverse events, and did not find any differences between groups in vital signs or laboratory values (Martini et al., 2022).

No reports of effects of sEH inhibitor treatment on cancer in humans were found but is an important safety issue to assess based on preclinical work and mechanistic knowledge.

***Drug interactions***:

Drug interactions of EC5026 have not yet been fully explored and/or published.

**Research underway:**

There is currently 1 study ongoing for EC5026 (NCT04908995). The trial is a Phase 1a single dose, double blind, placebo-controlled trial of 8 mg of EC5026 in healthy subjects. The study endpoints are safety, tolerability, food effects, and pharmacokinetics in order to better plan clinical trials for multiple dosing studies in healthy patients and in patients with pain.

**Search terms:**
Pubmed, Google: EC5026, soluble epoxide hydrolase inhibitor

- Drug interactions, dementia, Alzheimer's, APOE4, blood pressure, cancer

Websites visited for EC5026:

- Clinicaltrials.gov
- PubChem