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.

Senicapoc

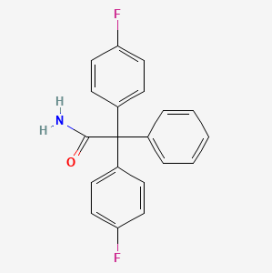
Evidence Summary

Senicapoc is a KCa3.1 blocker. Preclinical work consistently links senicapoc or related compounds to anti-neuroinflammatory effects. There is sparse clinical evidence, but there is an ongoing trial in AD.

Neuroprotective Benefit: Independent groups report elevations of KCa3.1 in neurodegenerative disease. Preclinically, senicapoc or related compounds reduce neuroinflammation and subsequent damage. These findings require clinical validation.

Aging and related health concerns: Preclinical work suggests potential for benefit of senicapoc in cancer and other diseases. Senicapoc clinical trials for asthma and COVID-19 have failed; a trial in glioblastoma is ongoing.

Safety: Gastrointestinal events like diarrhea and nausea appear to be the most common adverse events for senicapoc. The published safety data is largely in patients with sickle cell disease; the safety profile in other disease populations is not yet known.

Availability: In clinical development	**Dose**: Dosing has not yet been optimized. Clinical trials have used loading doses of up to 80 mg twice a day for 3 days and maintenance doses between 10 and 40 mg.	**Chemical formula:** $C_{20}H_{15}F_2NO$ **MW**: 323.3 g/mol  Source: PubChem
Half-life: 12.8 days	**BBB**: Penetrant.	
Clinical trials: In total, over 500 individuals have enrolled in trials of senicapoc.	**Observational studies**: No observational studies of senicapoc were identified.	

What is it?

$K_{Ca}3.1$ is a voltage-independent intermediate-conductance calcium-activated potassium channel coded for by the *KCNN4* gene. These channels are found in vascular endothelial cells, epithelial cells in some tissues like the lung, and in hematopoietic cells such as mast cells, macrophages, and microglia, among others (Wulff & Castle, 2010). $K_{Ca}3.1$ plays a key role in modulating calcium levels in cells. Elevated cellular calcium levels underpin many critical cellular processes. However, influx of calcium into cells depolarizes the membrane, reducing the driving force for calcium. Calcium activates $K_{Ca}3.1$, leading to efflux of potassium. This efflux contributes to repolarization of the membrane and thus facilitates the continued entry of calcium into the cell (Van der Velden et al., 2013). The increased intracellular calcium concentration can lead to a variety of downstream cellular processes, such as cellular proliferation and production of inflammatory chemokines and cytokines (Wulff & Castle, 2010). Through regulating calcium levels, $K_{Ca}3.1$ is involved in cytokine production and cellular proliferation, activation, and migration, along with volume regulation in erythrocytes (Nguyen et al., 2017), as well as fibrosis in different organs (Oliván-Viguer et al., 2017).

Senicapoc is a $K_{Ca}3.1$ inhibitor initially developed by Icagen. It has been tested in clinical trials for sickle cell disease, asthma, and COVID-19 (Granfeldt et al., 2022), though it has no approved uses. As of the writing of this report, it appears that different institutions hold the patent for different indications for this compound.

Neuroprotective Benefit: Independent groups report elevations of KCa3.1 in neurodegenerative disease. Preclinically, senicapoc or related compounds reduce neuroinflammation and subsequent damage. These findings require clinical validation.

Types of evidence:

- 5 reviews
- Numerous laboratory studies

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

There are no published studies that have explored any potential effect of senicapoc on cognitive function and/or prevention of dementia or decline.

Human research to suggest benefits to patients with dementia:

No published studies have investigated the effects of senicapoc in patients with dementia.

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

Neuroinflammation is thought to be a key player in Alzheimer's disease, and approaches to effectively modulate inflammatory responses are of great interest to the field (Heneka et al., 2025). By regulating calcium entry, microglial $K_{Ca}3.1$ is involved in oxidative burst, production of pro-inflammatory mediators like nitric oxide, and microglial-mediated neuronal killing (Maezawa et al., 2012).

It is important to recognize that inflammatory processes in AD and other diseases are very complex, and immune cell activities can be helpful and harmful in disease, depending on the specific activities and context. A treatment approach may be most effective if it targets deleterious glial processes while sparing beneficial glial activities, neurons, and more general immune function. $K_{Ca}3.1$ is primarily found on microglia and to some extent on astrocytes and is thought to be generally absent from neurons (Maezawa et al., 2012), though there is some controversy in the field as to the exact expression patterns of $K_{Ca}3.1$ (Yi et al., 2016). Preclinical work suggests that blocking $K_{Ca}3.1$ appears to reduce neurotoxic microglial activities while sparing their phagocytic capabilities (Kaushal et al., 2007; Jin et al., 2019). Jin

et al., 2019 reported that $K_{Ca}3.1$ transcript and protein levels are increased in the 5xFAD animal model of AD compared to wildtype littermate controls. They also found that levels of $K_{Ca}3.1$ protein are increased in tissue samples from the superior temporal cortex of 13 patients with AD and Braak stage 5 and 6, compared to 9 age-matched control individuals with Braak stage 0-2. Yi et al., 2016 also reported higher expression of $K_{Ca}3.1$ in brain sections from 6 patients with AD compared to 6 controls as assessed by qualitative assessment of IHC images. Furthermore, they report that levels of $K_{Ca}3.1$ in mice increase with age, and more significantly increase in SAMP8 mice which are a model of accelerated aging.

Some early preclinical work suggests that $K_{Ca}3.1$ blockers like senicapoc or TRAM-34 may exert beneficial effects in AD and other neurodegenerative diseases.

Jin et al., 2019 used primary microglial cultures, hippocampal slices, and mice to explore the effects of senicapoc; the researchers re-synthesized senicapoc for this study. Treating primary microglial cultures with senicapoc led to reductions in microglial proliferation, transcript levels of IL-1β, IL-6, and iNOS, levels of nitric oxide, and activation of p38MAPK. The group then treated 6-month-old 5xFAD mice with oral senicapoc for 3 months. At the end of dosing, they found that senicapoc treated mice had reduced microglial activation as measured by immunoreactivity of CD11b, Iba-1, and CD68 compared to control mice. Senicapoc treated mice also had lower transcript levels of IL-1β, TNF-α, IL-6, and iNOS and well as a decrease in amyloid deposition. They also found that senicapoc treatment mitigated the deficits in hippocampal LTP observed in control treated 5xFAD mice as measured by recordings from hippocampal slices. One limitation of the study is that they did not identify significant differences in memory performance at 9 months between their control 5xFAD mice and wildtype littermate controls, so the authors were unable to investigate the impact of senicapoc on cognitive function.

Yi et al., 2016 had previously found that inhibition or genetic deletion of $K_{Ca}3.1$ reduced astrogliosis. In this 2016 publication, they explored the effects of abrogating $K_{Ca}3.1$ function in the senescence-accelerated mouse prone 8 (SAMP8) mouse model of accelerated aging. They found that treating 7-month-old SAMP8 mice with one of two doses of TRAM-34 for 4 weeks lead to improvements in spatial learning and memory as measured by Morris water maze compared to vehicle treated mice, with a dose dependent response. In SAMP8 mice, treatment with TRAM-34 also led to decreases in GFAP and Iba1 staining compared to vehicle treatment, and more NeuN+ neurons were identified in the TRAM-34 group compared to the vehicle treatment group. The researchers then treated 8- to 10-week-old wildtype and $K_{Ca}3.1$ knockout mice with intrahippocampal injections of $A\beta_{1-42}$ oligomers. They found that post-injection with the oligomers, wildtype mice had spatial learning and memory performance deficits.

K_{Ca}3.1 knockout mice had attenuated deficits compared to the wildtype mice. The researchers also found fewer GFAP+ astrocytes and Iba1+ microglia as well as reduced neuronal loss in the treated knockout mice compared to treated wildtype mice. In *in vitro* experiments, the researchers found that application of Aβ oligomers to cultured astrocytes led to increases in intracellular free calcium. Genetic knockout of K_{Ca}3.1 or application of TRAM-34 abolished the increase in intracellular free calcium.

Inhibiting K_{Ca}3.1 with senicapoc and TRAM-34 has also been reported to have beneficial effects in animal models of Parkinson's disease (PD). Lu et al., 2019 describes experiments using MPTP as an inducible PD model in wildtype and K_{Ca}3.1 knockout mice. They found that K_{Ca}3.1 expression increased in the substantia nigra after MPTP treatment, and that treatment with senicapoc attenuated motor deficits and dopaminergic cell loss seen with MPTP treatment; they saw similar results in K_{Ca}3.1 knockout mice. Both K_{Ca}3.1 knockout and senicapoc treatment reduced microglial activation and upregulation of the pro-inflammatory compounds iNOS, COX-2, TNF-α, IL-6, and IL-1β in MPTP-treated mice. The researchers also found that compared to vehicle treatment, senicapoc treatment and K_{Ca}3.1 knockout reduced ER stress in total brain and in primary microglial cultures after MPTP or MPP+ treatment, respectively. In MPTP-treated mice, K_{Ca}3.1 knockout or senicapoc treatment reversed the suppression of the AKT/mTOR pathway seen in MPTP + vehicle treated mice.

A pre-print article from Samidurai et al., 2025 reported that levels of K_{Ca}3.1 are higher in brain sections of the substantia nigra from patients with dementia with Lewy bodies (DLB) or PD compared to age-matched controls. Like Lu et al., 2019, Samidurai and colleagues found that treatment of senicapoc reduced levels of inflammatory markers like TNF-α and IL-1β as well as mitigated dopaminergic neuron loss in an MPTP mouse model of PD. Treatment with TRAM-34 mitigated motor deficits in an α-synuclein pre-formed fibril (PFF) mouse model. They also reported that K_{Ca}3.1 knockout mice had reduced microglial activation and mitigated deposition of α-synuclein in a human α-synuclein-AAV-induced model of synucleinopathy.

K_{Ca}3.1 has also been implicated in other neurological insults. For instance, treatment with senicapoc mitigated tactile allodynia after peripheral nerve injury in rats (Staal et al., 2017). K_{Ca}3.1 expression in astrocytes has been reported to increase after spinal cord injury in mice, and inhibiting K_{Ca}3.1 with TRAM-34 improved locomotor function and neuronal survival (Bouhy et al., 2011). Similarly, treating mice with TRAM-34 after optic nerve transection reduced degeneration of retinal ganglion cells (Kaushal et al., 2007). TRAM-34 also mitigated cognitive impairment and microglial activation in a mouse model of post-operative cognitive decline (Saxena et al., 2023) and reduced mRNA levels of pro-inflammatory

molecules such as TNF-α as well as protected against experimental autoimmune encephalomyelitis (EAE) in a mouse model of multiple sclerosis (Reich et al., 2005).

Inhibiting $K_{Ca}3.1$ with TRAM-34 in a rat model of ischemic injury and reperfusion stroke reduced the infarct volume, neurological deficit, and microglial activation (Chen et al., 2011). The research group replicated the results with senicapoc and found that senicapoc similarly reduced infarct volume, microglial activation, neuronal loss, inflammatory markers like IL-1β, IL-6, and TNF-α, and neurological deficit (Lee et al., 2024). Both Chen et al., 2011 and Lee et al., 2024 reported the beneficial effects of TRAM-34 and senicapoc when they were administered 12 hours after the ischemic event. Other $K_{Ca}3.1$ inhibitors have also been reported to reduce infarct volume and brain swelling in a rat model of traumatic brain injury (Mauler et al., 2004). One study by Chen et al., 2015 also reported that $K_{Ca}3.1$ is present on blood-brain barrier endothelial cells in various animals, including humans, and that TRAM-34 treatment reduced brain edema in a rat model of ischemia.

It is worth noting that TRAM-34 is also blood-brain barrier penetrant and is used in rodent studies, but it is not ideal for clinical use due to its short half-life and lack of oral bioavailability; the effects of TRAM-34 and senicapoc have been reported to be similar (Jin et al., 2019); both inhibit the channel by fully or partially occupying the site where potassium would otherwise bind before entering the selectivity filter (Nguyen et al., 2017).

APOE4 interactions:

It is not known whether there are any interactions between senicapoc and APOE status.

Aging and related health concerns: Preclinical work suggests potential for benefit of senicapoc in cancer and other age-related diseases, but no clinical studies have been run or completed. Senicapoc failed clinical trials for asthma and COVID-19.

Types of evidence:

- 2 randomized controlled clinical trials
- 1 open label trial
- 4 reviews
- Numerous laboratory studies

Respiratory Function, Including Asthma and COVID-19: NO PROVEN BENEFIT

Preclinical studies in animal models of acute respiratory syndrome have shown improvements in respiratory function after administration of senicapoc (Petersen et al., 2021; Petersen et al., 2022). However, a small open-label study of senicapoc in 48 patients with severe COVID-19 did not find any improvement in respiratory function after two doses of 50 mg senicapoc compared to standard of care treatment. There were indicators of reduced respiratory function in the senicapoc group 72 hours after dosing compared to the standard of care group, though technical confounds rather than study medication may account for this result. While there were numerical differences between the two groups in terms of 28-day mortality, baseline differences in disease severity and small study size make it difficult to ascribe these changes to senicapoc (Granfeldt et al., 2022).

Senicapoc has also been tested in patients with asthma. The results have been announced in press releases but have not been published in a peer-reviewed journal. As reported on a news site, a trial enrolled 34 patients with asthmatic responses to inhaled allergens and randomized them to receive either senicapoc or placebo. Participants received a loading dose of 80 mg twice daily of senicapoc or matching placebo for 3 days and then a maintenance dose of 40 mg once per day for the remaining 11 days of the treatment period (NCT00861211). An allergen challenge was administered at baseline and at the end of the treatment period. Patients treated with senicapoc had an attenuated late-phase allergen response and decreased concentration of exhaled nitric oxide, indicating that senicapoc was modulating asthmatic disease (FierceBiotech news article).

However, a subsequent trial failed to show any benefit of senicapoc for exercise induced asthma. The trial (NCT00861185) enrolled 69 patients with exercise-induced asthma and randomized them to receive either senicapoc or placebo. Participants in the senicapoc group received a loading dose of 80 mg twice daily for 3 days, followed by maintenance dosing of 40 mg once daily for the rest of the 4-week dosing; placebo patients received placebo pills on the same dosing schedule. The primary outcome was a measurement of respiratory function after exercise. There was no difference between groups. The company announced that while they would continue to analyze the data collected, that they did not anticipate continuing clinical development of this compound (FierceBiotech news article).

Preclinical studies have also suggested that senicapoc may have utility in pulmonary fibrosis (Roach & Bradding, 2020).

Cancer: POTENTIAL FOR BENEFIT

K_{Ca}3.1 can contribute to cell cycle progression and cellular proliferation and has been implicated in several kinds of cancer including pancreatic, endometrial, breast, prostate, colorectal, and liver cancer, among others (reviewed by Calderón Artavia & Arvelo Álvarez, 2024). Levels of K_{Ca}3.1 are prognostic in at least some types of cancer, such as lung cancer (Ko et al., 2019) and glioblastoma (Brown et al., 2018). Treating cancer cell lines with senicapoc has been shown to induce apoptosis and reduce migration (Todesca et al., 2024), and treatment with TRAM-34 has reduced tumor infiltration (Brown et al., 2018) and slowed tumor growth ((Wulff & Castle, 2010) in animal xenograft models. An ongoing clinical trial is testing mono- and combination therapy of senicapoc and another drug called perampanel in 36 patients with glioblastoma (NCT07284069).

Other potential indications based on preclinical work:

Preclinical studies have reported benefits of senicapoc or pharmacological inhibition of K_{Ca}3.1 in various other disease models. For instance, treatment with TRAM-34 was reported to reduce renal fibrosis in mice and rats, and renal injury in a mouse model of established diabetic nephropathy, as reviewed by Roach & Bradding, 2020. In a high-fat diet animal model of MASLD, treatment with senicapoc reduced hepatic fat and decreased fibrosis (Paka et al., 2017), though it should be noted that another study found that inhibition of K_{Ca}3.1 worsened liver damage in a rat model of liver injury (Sevelsted Møller et al., 2016; reviewed by Roach & Bradding, 2020). Treatment with TRAM-34 also mitigated atherosclerotic plaque development in a diabetic mouse model (Jiang et al., 2022; reviewed by Roach & Bradding, 2020). Several animal studies have reported decreases in blood pressure after administration of senicapoc, but human studies have not reported these effects (Wulff & Castle, 2010).

These findings speak to the potential for broad anti-inflammatory utility of K_{Ca}3.1 inhibitors, but clinical studies are needed to explore whether these preclinical effects have any parallel in humans.

Senicapoc has been explored or posited as a treatment for other diseases that are not age-related, including sickle cell disease (Ataga et al., 2011) and malaria (Tubman et al., 2015).

Safety: Gastrointestinal events like diarrhea and nausea appear to be the most common adverse events for senicapoc. The published safety data is largely in patients with sickle cell disease; the safety profile in other disease populations is not yet known.

Types of evidence:

- 3 randomized controlled clinical trials
- 3 laboratory studies

Senicapoc has been tested in patients with sickle cell disease, asthma, and COVID-19, and is often described as well-tolerated in the literature (Wulff & Castle, 2010). Gastrointestinal events like diarrhea and nausea appear to be among the most common. However, safety data in relatively healthy patients is lacking, as is data in elderly or cognitively impaired populations. Long-term safety data past two years is also needed.

Ataga et al., 2011 describes a phase III randomized controlled trial of senicapoc in 297 patients with sickle cell disease who were 16 to 65 years of age. Participants randomized to the senicapoc group received a loading dose of 20 mg twice daily for 4 days, followed by a maintenance dose of 10 mg daily for the remainder of the 52-week trial; participants in the placebo group received placebo pills in the same fashion. Study medication was taken by mouth. The trial included patients who were receiving concomitant therapy with hydroxycarbamide, also known as hydroxyurea, an approved sickle cell disease therapy. Of the 289 patients who received at least one dose of study medication, 165 of them received concurrent treatment with hydroxycarbamide and 126 did not. An interim analysis by a data monitoring committee recommended that patients not on concurrent hydroxycarbamide be removed from the trial and that all future enrollees be on hydroxycarbamide, and a subsequent interim analysis led to early study termination due to the unlikelihood of reaching the primary efficacy endpoint. More than half of the patients received senicapoc for ≥7 months, and more than 25% completed the year of dosing.

Frequency of experiencing at least one treatment-emergent adverse event was similar between the senicapoc and placebo group (87% vs. 83%, respectively). Nausea (16% vs. 10%) and urinary tract infection (14% vs. 8%) were more common in the senicapoc group compared to the placebo group, respectively. Some events were more common in the placebo group, such as upper respiratory tract infection (8% vs. 14%). A similar proportion of each group withdrew from the study due to an adverse event (8% vs. 6%); sickle cell crisis related events accounted for one drop out in the placebo group and

four in the senicapoc group. There were two deaths in the study, both in the placebo group and both deemed unrelated to study drug. There were more frequent elevations in alkaline phosphatase, gamma-glutamyl transferase, hemoglobin, and platelets in the senicapoc group compared to the placebo group. There were also more frequent elevations of creatinine, bilirubin, and LDH in the placebo group compared to the senicapoc group. There were no clinically relevant changes in vital signs or physical examination.

A phase 2 study randomized 90 patients with sickle cell disease to receive low-dose senicapoc (6 mg per day), high-dose senicapoc (10 mg per day), or placebo for 12 weeks. Of these patients, 10 withdrew from the study. Three discontinuations were due to adverse events: one for weakness and shortness of breath in the low-dose group, and two for pain crises and acute chest syndrome in the high-dose group. Diarrhea and nausea were more frequent in the treatment group, and the adverse event frequency appeared to be dose related. All of these gastrointestinal events were mild or moderate in severity. There were serious adverse events in the study including sickle cell crisis, pneumonia, and acute chest syndrome, but no serious adverse event was attributed to senicapoc. The serious adverse events were distributed between groups. There were no clinically meaningful changes in vital signs, physical examinations, or electrocardiograms. There was an increase in median GGT value in both low-dose and high-dose groups compared to placebo (Ataga et al., 2008).

Senicapoc development for sickle cell disease was discontinued after these phase III results, though it should be noted that senicapoc did have the predicted molecular events even though it did not reduce sickle cell pain crisis events that were the primary outcome of the study (Ataga et al., 2021).

Senicapoc has also been tested in patients with COVID-19 in a small randomized open label study. The trial randomized 48 patients admitted to the ICU with severe respiratory insufficiency to receive senicapoc or standard of care treatment. Those randomized to the intervention received 50 mg of enteral senicapoc as soon as possible after randomization and then another 50 mg dose 24 hours later. The publication only included serious adverse events, none of which were linked to the study medication. Compared to the standard of care group, the senicapoc group had a lower frequency of cardiac arrhythmia (10% vs. 23%), requirement of renal therapy (0% vs. 19%), and death within 28 days (10% vs. 23%). However, there were more patients in the control group who required ventilation at baseline (54% compared to 35%), indicating that the standard of care group had more severe illness at baseline and might account for these differences (Granfeldt et al., 2022). While senicapoc was tested in two trials for asthma, safety data was not publicized for these trials.

Drug interactions:

The drug interactions of senicapoc are not yet known.

Research underway:

There are 4 ongoing clinical trials of senicapoc registered on clinicaltrials.gov. One trial is in patients with fibrotic interstitial lung disease; one in patients with sickle cell anemia, and one in patients with glioblastoma. One trial is in patients with AD.

NCT04804241 is an ongoing clinical trial that aims to enroll up to 55 patients with early AD. Participants are randomized to receive either 10 mg per day of senicapoc by mouth or matching placebo for 52 weeks. Data for primary efficacy measures will be collected at baseline, week 26, and week 52, with additional safety monitoring visits at week 4, 12, and 36. Patients will have one more visit at week 78, 26 weeks after dosing ends, to allow a full wash-out period. The primary outcome measures are change in cognition as measured by ADAS-Cog, change in CSF biomarkers IL-1β, IL-6, TNF-α, MCP-1, and IL-10, and serum biomarkers IL-6, TNF-α, MCP-1, IL-10, and high sensitivity CRP. There are more than a dozen secondary outcome measures, including assessments of cognition, structural outcomes as measured by MRI, and amyloid PET. The study is estimated to complete in June 2026

Search terms:
Pubmed, Google: senicapoc

- Cognitive function, dementia, asthma, COVID-19, cancer

Websites visited for senicapoc:

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

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.