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.

SFX-01 (Sulforadex®)

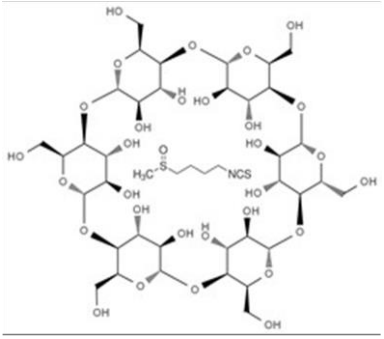
Evidence Summary

Same general benefit profile as sulforaphane but offers the advantage of dose titration because it is a non-dietary source with high bioavailability.

Neuroprotective Benefit: No direct evidence for SFX-01 but is expected to offer same neuroprotective benefits as sulforaphane.

Aging and related health concerns: Potential benefit in cancer prevention, like sulforaphane, and in cancer treatment as combination therapy.

Safety: Good safety profile, though limited number of studies. High doses are associated with gastrointestinal problems.

Availability: Clinical trials	**Dose**: 300 mg 2X daily (12 hours apart) orally	**Chemical formula:** $C_6H_7NO_3S + C_{36}H_{60}O_{30}$ (Sulforaphane + alpha-cyclodextrin) **MW**: 173.19 + 972.846 g/mol
Half-life: 2-3 hours (same as Sulforaphane	**BBB**: Penetrant (for Sulforaphane in animals)	
Clinical trials: 1 Phase 2 trial in breast cancer (ongoing).	**Observational studies**: None	 Source: Evgen Pharma

What is it? SFX-01 (Sulforadex®) is a **synthetic sulforaphane** which is stabilized by an alpha-cyclodextrin ring [1]. The alpha-cylcodextrin (Alfadex) is therapeutically inert and has a lipophilic core which stabilizes the lipophilic sulforaphane, but is overall water-soluble, which greatly enhances the bioavailability of sulforaphane. Once SFX-01 enters the gastrointestinal-system, the alpha-cyclodextrin ring is cleaved and the sulforaphane is released to exert its effects in the body. Sulforaphane is the most potent known natural activator of the Nrf2 antioxidant pathway. SFX-01 is currently being tested in clinical trials for breast cancer and subarachnoid hemorrhage following stroke.

Neuroprotective Benefit: No direct evidence for SFX-01 but is expected to offer same neuroprotective benefits as sulforaphane.

Types of evidence:

- None

No studies have been performed in humans or animals testing the neuroprotective effects of SFX-01. Sulforaphane has been shown to have neuroprotective antioxidant properties in cell culture and

improve cognition in rodent Alzheimer's disease models (see Sulforaphane report). Since SFX-01 is just a synthetic stabilized form of sulforaphane with increased bioavailability, it is expected to have the same neuroprotective ability as natural sulforaphane.

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

Expected to be the same as sulforaphane (Nrf2 antioxidant pathway activation).

APOE4 interactions: Unknown

Aging and related health concerns: Potential benefit in cancer prevention, like sulforaphane, and in cancer treatment as combination therapy.

Types of evidence:

- 1 clinical trial (Phase 2 open-label trial for breast cancer)
- Several laboratory studies

Breast Cancer: Potential benefit

An open-label Phase 2 trial (STEM NCT02970682) (n=60) testing SFX-01 (300 mg BID) in estrogen receptor+ anti-estrogen therapy resistant metastatic breast cancer patients is currently underway and expected to be completed in March 2019. An interim report of the first 20 patients indicated potential therapeutic benefit in that 4 patients had disease stabilization for the study duration (24 weeks), and one had a partial response with 30% tumor reduction. Based on these results, patients will continue SFX-01 treatment through the compassionate use program.

Rodent and cell culture studies provide evidence toward a potential mechanism. In rodent metastatic breast cancer tumor xenograft models, SFX-01 treatment (300 mg/kg daily oral gavage) inhibited tumor growth (P=0.02 compared to vehicle) and the formation of lung micrometastasis [2]. Most notably, SFX-01 augmented the anti-tumor response of tamoxifen (P=0.007 vs tamoxifen alone) **in the context of anti-estrogen therapy resistant breast cancer.** In primary metastatic breast cancer cells, SFX-01 treatment reduced the growth of ALDH+ cancer stem cells. Tumor cells from patients that develop anti-estrogen therapy resistance increase pSTAT3 [2] and canonical Wnt signaling [3]. SFX-01 decreases pSTAT3 [2] and Wnt signaling [3], which may underlie its therapeutic effects.

Osteoarthritis: Potential minor benefit (mice)

Treatment with SFX-01 (100 mg/kg/day orally) for 3 months was moderately beneficial in a strain of mice (STR/Ort) that develop spontaneous osteoarthritis [4]. It partially corrected gait asymmetry, though only one of the 8 principal components of gait was significantly different ($P<0.05$). It also increased bone area (noted shift in balance between bone formation and reabsorption markers) and bending strength in some bones but not others. SFX-01 had no beneficial effect on cartilage pathology. Suggests that benefits for SFX-01 supplementation are likely to be tissue-type specific and will not provide equal protection from oxidative stress damage throughout the body.

Safety: Good safety profile, though limited number of studies. High doses are associated with gastrointestinal problems.

Types of evidence:

- 3 clinical trials (2 Phase 1 RCTs, 1 Phase 2 open-label trial)
- Several laboratory studies

No adverse effects have been reported in clinical studies in doses up to 300 mg. The highest dose tested was 700 mg, which was associated with gastrointestinal-related adverse events, particularly vomiting when taken in the fasted state. Taking SFX-01 with food reduces side-effects without negatively impacting pharmacokinetics. Peak plasma levels occur ~ 1 hour after oral administration. Based on a rat study, the bioavailability of SFX-01 is 78% [5].

Sulforaphane, the active substance in SFX-01 has a good safety profile, though the effects of long-term supplementation are not known.

Sources and dosing:

600 mg is expected to be the therapeutic dose based on Phase I trials (NCT01948362, NCT02055716). The recommended dosing is 300 mg 2X daily, since this was associated with fewer adverse events than the 600 mg 1X daily dose.

Sulforadex® (SFX-01) is the propriety technology of Evgen Pharmaceuticals.

Research underway:

Phase 2 (STEM NCT02970682) open-label trial in ER+ anti-estrogen therapy resistant breast cancer for SFX-01 in combination with anti-estrogen therapy.

Phase 2 RCT (SAS NCT02614742) for the prevention of spontaneous subarachnoid hemorrhage (age 18-80). Patients will be treated with nimodipine (standard of care) + SFX-01(300 mg BID) starting 48 hours after stroke for up to 28 days. The trial is expected to be completed in April 2019.

Search terms:

Pubmed, Google: Sulforadex (or SFX-01) + clinical trials, neuroprotection, neurodegeneration, aging, cancer, cardiovascular, safety, meta-analysis, Nrf2

Websites visited for SFX-01:

- Clinicaltrials.gov
- PubChem (sulforaphane, alpha-cyclodextrin)
- Evgen.com

References:

1. Pharma E (2018). http://evgen.com/

2. Simões BM, Denis A, Eyre R *et al.* (2016) Sulforadex targets breast cancer stem-like cells in patient-derived cells and xenograft tumours. *European Journal of Cancer* 61, S77.https://doi.org/10.1016/S0959-8049(16)61269-8

3. Howell S, Simoes B, Alferez D *et al.* (2017) Abstract PD2-02: SFX-01 targets Wnt signalling to inhibit stem-like cells in breast cancer patient-derived xenograft tumours. *Cancer Research* 77, PD2-02-PD02-02

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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.