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.

Cutamesine

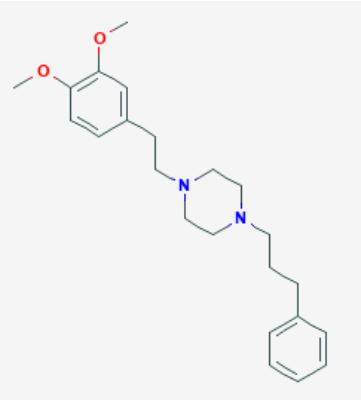
Evidence Summary

Cutamesine has been tested for depression and stroke recovery but has not advanced to phase 3 trials. Preclinical studies suggest cognitive and neuroprotective benefit.

Neuroprotective Benefit: Based on PET imaging studies, sigma 1 receptors appear to be decreased with Alzheimer's disease. Cutamesine treatment in preclinical models improved cognitive functions, increased BDNF, and prevented neuronal death.

Aging and related health concerns: Cutamesine failed to improve the primary efficacy measure in ischemic stroke patients, but potential benefits were seen in severe patients. Preclinical studies suggest benefit against cardiac hypertrophy and neuropathy.

Safety: Cutamesine treatment for 4 weeks was well-tolerated in a phase 2 trial of stroke patients, but safety data from large, long-term studies are lacking.

Availability: In clinical development	**Dose**: The phase 2 trial in acute ischemic stroke patients tested cutamesine doses of 1 or 3 mg/day.	**Chemical formula:** $C_{23}H_{32}N_2O_2$ **MW**: 368.5  Source: PubChem
Half life: not documented	**BBB**: penetrant	
Clinical trials: The phase 2 trial in major depressive disorder enrolled 150 participants. The phase 2 trial in acute ischemic stroke patients included 60 patients.	**Observational studies**: Several small studies have used radiolabeled cutamesine to show levels of sigma 1 receptor in the brains of Alzheimer's patients, Parkinson's patients, and healthy controls.	

What is it? Cutamesine is a sigma 1 receptor agonist originally developed by Santen Pharmaceutical, Japan, for the treatment of cognitive diseases. Sigma 1 receptors are chaperone proteins at the endoplasmic reticulum (ER) and modulate calcium signaling through the IP3 receptor. Sigma 1 receptors also control calcium release from the ER into mitochondria (Ono et al., 2014). Sigma 1 receptor activation can improve memory, promote cell survival, and exert antidepressant-like actions (Fujimoto et al., 2012). Sigma 1 receptors may also play a role in several central nervous system disorders, including schizophrenia, depression, dementia, and ischemia (Toyohara et al., 2009).

Cutamesine has been tested in phase 2 trials in major depressive disorder and in patients recovering from stroke (NCATS Inxight). In 2016, cutamesine was under development by M's Science Corporation, Japan, for amyotrophic lateral sclerosis (ALS Research Forum).

Neuroprotective Benefit: Based on PET imaging studies, sigma 1 receptors appear to be decreased with Alzheimer's disease. Cutamesine treatment in preclinical models improved cognitive functions, increased BDNF, and prevented neuronal death.

Types of evidence:

- 0 clinical trials
- 3 observational studies, examining sigma 1 receptor levels with PET [11C]SA4503 imaging
- Numerous laboratory studies

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

Human research to suggest benefits to patients with dementia:
In a study using radiolabeled cutamesine ([11C]SA4503), sigma 1 receptors were distributed throughout the brain in normal subjects, but were decreased in the frontal, temporal, and occipital lobes, cerebellum, and thalamus in patients with early Alzheimer's disease and in the putamen in patients with Parkinson's disease (Toyohara et al., 2009). Similarly, in a study of 5 Alzheimer's patients and 7 controls, PET imaging of [11C]SA4503 showed that binding potential in Alzheimer's patients was significantly lower in the frontal, temporal, and occipital lobe, as well as the cerebellum and thalamus (Mishina et al., 2008).

In contrast, in a more recent study of PET [11C]SA4503, no significant differences were found in Parkinson's patients compared to healthy controls (Wilson et al., 2020). No changes were seen longitudinally either, comparing follow-up PET imaging with baseline imaging.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Cutamesine has been studied in several animal models of cognitive impairment.

Animal models: In a rat model of memory impairment induced by scopolamine, cutamesine treatment (0.05, 0.1, or 0.25 mg/kg, orally) reduced the memory impairment (Senda et al., 1996). Repeated administration of cutamesine after basal forebrain lesion also ameliorated memory impairment.

In a rat model of spatial learning impairment induced by basal forebrain lesion, cutamesine treatment (0.25 mg/kg, orally) for 13 days ameliorated learning deficit as measured by the Morris water maze (Senda et al., 1998).

In a mouse model of memory impairment induced by the non-competitive NMDA receptor antagonist dizocilpine, cutamesine treatment (0.03-1 mg/kg, s.c.) attenuated memory deficits measured by the Y-maze and step-down passive avoidance tests (Maurice and Privat, 1997).

In a mouse model of α-thalassemia X-linked intellectual disability syndrome, cutamesine treatment (1 mg/kg, i.p.) for 2 weeks rescued cognitive deficits as measured by the Y-maze test and reversed axonal development and dendritic spine abnormalities (Yamaguchi et al., 2018). Cutamesine treatment also restored the decreased levels of BDNF in the medial prefrontal cortex. In contrast, these mice treated with vehicle had significantly higher immature spine protrusions, significantly longer spine necks, significantly shorter axonal length, significantly greater number of filopodia, and significantly lower mature spine protrusions.

In a rat model of REM sleep deprivation, cutamesine treatment (1 mg/kg) occupied 92% of the sigma-1 receptors while reversing the sleep deprivation-induced cognitive deficit as measured by the passive avoidance test (Ramakrishnan et al., 2015). A lower dose (0.3 mg/kg) occupied 88 % of the receptors but did not significantly improve cognition—and the reasons for this discrepancy are unclear.

In a mouse model of ALS (SOD1 G93A mice), cutamesine treatment (1 mg/kg/day, s.c.) started at 5 weeks old until time of death significantly extended the survival time compared to vehicle treatment, even though the treatment did not affect the time of pathology onset (Ono et al., 2014). In NSC34 cells exposed to SOD1G93A, cutamesine treatment prevented cell death in a concentration-dependent manner. Cutamesine upregulated protein levels of phosphorylated Akt and phosphorylated ERK1/2.

In normal rats, cutamesine treatment (0.3, 1, or 3 mg/kg, i.p.) for 2 or 4 weeks increased BDNF levels in the hippocampus but not in the frontal cortex; this increase was not seen with a single injection (Kikuchi-Utsumi and Nakaki, 2008). The 1 mg/kg dose for 2 weeks showed the most pronounced 2-fold increase of BDNF protein levels in the hippocampus, while the 3 mg/kg dose did not increase BDNF further.

In vitro studies: In cultured cortical neurons, cutamesine pretreatment partly inhibited H2O2-induced neuronal cell death (Tuerxun et al., 2020). H2O2 triggers a series of events including over-activation of

MAPK/ERK and intracellular calcium accumulation via voltage-gated calcium channels and ionotropic glutamate receptors, resulting in neuronal cell death. In contrast, cutamesine treatment reduced the activation of the MAPK/ERK pathway and downregulated the ionotropic glutamate receptor subunit, GluA1.

In cultured hippocampal neurons, cutamesine treatment enhanced axonal length which was accompanied by the inhibition of voltage-gated Ca2+ influx (Li et al., 2017).

In cultured embryonic spinal neurons from a mouse model of ALS (G93A hSOD1 mice), cutamesine treatment accelerated cytosolic Ca2+ clearance following kainate activation of AMPA receptors and IP3R-mediated ER Ca2+ release following bradykinin stimulation (Tadic et al., 2017). Interestingly, a different sigma 1 receptor agonist (PRE-084) did not exert any significant effects on cytosolic Ca2+. Chronic treatment with cutamesine in rat B104 neuroblastoma cells caused a time- and dose-dependent potentiation of the secretion of BDNF without affecting the mRNA levels of BDNF (Fujimoto et al., 2012). Cutamesine decreased intracellular levels of pro-BDNF and mature BDNF whereas increased the extracellular levels of mature BDNF.

In an *in vivo* brain microdialysis study in rats, cutamesine treatment significantly enhanced acetylcholine release in the frontal cortex as well as the hippocampus, but not the striatum (Kobayashi et al., 1996).

A single dose of the Alzheimer's medication, donepezil, bound to sigma 1 receptors with occupancies of 60-75%, depending on the dose (Ishikawa et al., 2009). This opens the possibility that sigma 1 receptors may play a role in the pharmacological mechanism of donepezil beyond its well-known inhibition of the acetylcholinesterase enzyme.

PET imaging studies: The findings are mixed with regards to age-related changes in sigma 1 receptor distributions and levels in rodents. One study reported that [3H]SA4503 specific binding was higher in 24-month-old rats compared to young rats (1.5-6.0 months) (Ishiwata et al., 2003). The increased sigma 1 receptor numbers were thought to be compensatory to the decreased binding affinity with aging. A different study reported that the distributions of sigma 1 receptors were altered with aging in rats and binding potential was reduced in the hypothalamus, pons, and medulla, while the cortex showed no age-related changes (Ramakrishnan et al., 2016).

APOE4 interactions: Unknown.

Aging and related health concerns: Cutamesine failed to improve the primary efficacy measure in ischemic stroke patients, but potential benefits were seen in severe patients. Preclinical studies suggest benefit against cardiac hypertrophy and neuropathy.

Types of evidence:

- 1 phase 2 clinical trial in stroke patients
- Several laboratory studies

Ischemic stroke: NO SIGNIFICANT BENEFIT, BUT POSSIBLE BENEFIT IN SEVERE PATIENTS
In a phase 2 double-blind randomized controlled trial in 60 acute ischemic stroke patients, cutamesine treatment (1 or 3 mg/day) for 28 days did not result in significant improvements in the primary efficacy measure (change in National Institutes of Health Stroke Scale from baseline to day 56) or modified Rankin Scale (neurological disability) and Barthel Index (activities of daily living)(Urfer et al., 2014). However, in a post hoc analysis of moderately and severely affected patients (baseline National Institutes of Health Stroke Scale, ≥7 and ≥10, respectively), the higher dose of cutamesine (3 mg/day) showed greater improvements in the National Institutes of Health Stroke Scale compared to the placebo group (p=0.034 and p=0.038, respectively).

When compared with the placebo group, a higher proportion of subjects treated with 3 mg/day cutamesine could complete a 10-meter timed walk on day 28 (82% versus 55%; p=0.079) and on day 56 (88% versus 67%; p=0.106), though these measures did not reach statistical significance (Urfer et al., 2014). This positive trend is slightly confounded by the cutamesine-treated groups showing numerically higher completion of walk % at baseline.

Cardiovascular diseases: POTENTIAL BENEFIT BASED ON RODENT MODELS
In a rat model of asphyxia cardiac arrest (induced by global cerebral ischemic/reperfusion injury), cutamesine treatment (1 mg or 2.5 mg/kg) resulted in improved neurological outcomes; small benefits were seen with the 1 mg/kg dose and significant improvement, closer to sham rats, were seen with the 2.5 mg/kg treatment (Qin et al., 2019). The protein levels of caspase-3 and the ER stress markers C/EBP homologous protein and caspase-12 were lower in the cutamesine-treated groups compared to untreated controls. Cutamesine treatment also normalized mitochondrial membrane potential, tissue ATP concentrations, intracellular calcium overload, and upregulated sigma 1 receptor protein levels compared with controls. Cutamesine high dose treatment (2.5 mg/kg) showed significant cerebral protective effects compared with the low dose (1 mg/kg) treatment. Cardiac arrest downregulated sigma 1 receptor protein expression, but cutamesine activation of sigma 1 receptors protected against

global cerebral ischemia/reperfusion injury by alleviating ER stress and mitochondrial dysfunction while inhibiting neuronal apoptosis.

In a mouse model of cardiac hypertrophy (transverse aortic constriction), cutamesine treatment (1 mg/kg, orally) for 4 weeks significantly inhibited angiotensin II-induced cardiomyocyte hypertrophy (Tagashira et al., 2013). Cutamesine treatment also decreased hypertrophy-induced impairments in left ventricular contractile function. Exposure of cardiomyocytes to angiotensin II for 72 hours decreased basal ATP content, phenylephrine-induced ATP production, and mitochondrial size, while cutamesine treatment restored ATP production and mitochondrial size.

Neuropathy: POTENTIAL BENEFIT BASED ON RODENT MODELS
Repeated treatment with chemotherapeutic agents induces neuropathic pain, which results in a significant reduction of sigma 1 receptor levels in the spinal cord (Mori et al., 2015). In a rat model of neuropathy (induced by chemotherapeutics oxaliplatin and paclitaxel), cutamesine treatment (3 mg/kg) potently inhibited the neuropathy while this effect was abolished by sigma 1 receptor antagonist, NE-100 (Mori et al., 2015). These results suggest that the reduction of sigma 1 receptor activity is involved in chemotherapeutic-induced neuropathy. Cutamesine did not alter nociceptive stimuli thresholds when rats were not exposed to chemotherapeutic agents.

Hearing loss: PROTECTED AGAINST NOISE-INDUCED, BUT NOT AGE-INDUCED HEARING LOSS BASED ON RODENT MODELS
In a mouse model of noise-induced hearing loss, cutamesine treatment (3 or 30 mg/kg; started 10 days before noise exposure and continued to end of study) protected hearing function (reduced threshold shifts) and prevented the cell death of fibrocytes within the spiral limbus (Yamashita et al., 2015). However, cutamesine did not prevent age-associated hearing loss. These results suggest that cutamesine treatment prior to noise exposure reduces noise-induced hearing loss and cochlear damage during the acute phase of noise-related damage. Cutamesine treatment after noise exposure increased sigma 1 receptor expression in the cochlea.

Safety: Cutamesine treatment for 4 weeks was well-tolerated in a phase 2 trial of stroke patients, but safety data from large, long-term studies are lacking.

Types of evidence:

- 2 clinical trials (of which 1 had results published in a peer-reviewed journal)

In a phase 2 double-blind randomized controlled trial in 60 acute ischemic stroke patients, cutamesine treatment (1 or 3 mg/day) for 28 days was safe and well tolerated without significant differences in numbers of treatment emergent or serious adverse events (Urfer et al., 2014). At least 1 treatment-emergent adverse event was reported in 17/19 subjects (90%) in the 1 mg/day cutamesine group, 15/19 subjects (79%) in the 3 mg/day cutamesine group, and 17/22 subjects (77%) in the placebo group. There was no clear relationship of treatment-emergent adverse event incidence to treatment or dose. The number of adverse events considered at least possibly related to the study drug did not differ significantly between groups, reported in 3 (16%) subjects receiving 1 mg/day cutamesine, 1 (5%) receiving 3 mg/day cutamesine, and 2 (9%) receiving placebo. There was 1 death 6 days after randomization due to cerebral hemorrhage, in a subject receiving 3 mg/day cutamesine. This event was considered unrelated to the study drug by the treating clinician. One serious adverse event (respiratory failure) was reported for 1 subject in the 1 mg/day cutamesine group. This event was also considered unrelated to the study drug. Two subjects in the 3 mg/d cutamesine group had a serious adverse event: one stroke that occurred after carotid endarterectomy and 1 instance of hemorrhagic transformation of stroke 1 day after randomization, neither of which were considered to be related to the drug. No serious adverse events were reported in subjects receiving placebo.

Drug interactions: Drug interactions have not been well studied.

Sources and dosing: Cutamesine is a sigma 1 receptor agonist originally developed by Santen Pharmaceutical, Japan, for the treatment of cognitive diseases. In 2016, cutamesine was under development by M's Science Corporation, Japan, for amyotrophic lateral sclerosis (ALS Research Forum). The phase 2 trial in acute ischemic stroke patients tested cutamesine doses of 1 and 3 mg/day (Urfer et al., 2014).

Research underway: There are currently no ongoing clinical trials testing cutamesine, based on ClinicalTrials.gov. There are also no studies funded by the National Institutes of Health that are testing cutamesine.

Search terms:

Pubmed, Google: cutamesine and SA4503

- + cognitive, + ApoE4, + clinical trial, + neuropathy, + stroke, +cardiovascular

Websites visited for cutamesine and SA4503:

- Clinicaltrials.gov (2)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)