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.

SBT-272

Evidence Summary

Some benefits are seen in rodent models of ALS, Parkinson's, and ischemic stroke, but no data in humans exist to date. Chronic toxicology studies and a phase I clinical study are underway.

Neuroprotective Benefit: SBT-272 shows significantly higher brain accumulation than SS-31 in rodent studies. SBT-272 has shown neuroprotective benefits in rodent models of ALS, Parkinson's, and ischemic stroke. No data on cognitive benefits exist to date.

Aging and related health concerns: No studies with SBT-272 have been carried out for age-related diseases.

Safety: No safety or toxicology studies have been published to date. In a mouse model of ALS, SBT-272 extended lifespan, suggesting long-term treatment in mice is likely safe. Chronic toxicology studies and a phase I clinical study are underway.

Availability: not available, under clinical development	**Dose**: not established; preclinical studies in rodents have used doses ranging from 0.5 to 5 mg/kg/day, i.p. In an ongoing phase I study in healthy people, SBT-272 is administered orally, though the dose range is not noted.	**Chemical formula:** structure not disclosed **MW**: not disclosed
Half life: not documented	**BBB**: penetrant based on preclinical studies	
Clinical trials: No clinical trials have been completed. In January 2020, a first-in-human phase 1 study of SBT-272 in 40 healthy subjects was initiated.	**Observational studies**: none available	

What is it? SBT-272 is a novel peptidomimetic drug under development for the treatment of amyotrophic lateral sclerosis (ALS) and multiple system atrophy (MSA), a neurological disorder leading to parkinsonism. SBT-272 is under development by Stealth BioTherapeutics Inc. The mechanism of action is similar to Stealth BioTherapeutic's first-in-class lead compound, SS-31 (also known as Elamipretide, Bendavia, and MTP-131). SBT-272 interacts with cardiolipin, a lipid exclusively expressed on the inner mitochondrial membrane that plays an important structural role in organizing the components of the electron transport chain into "supercomplexes" for more efficient oxidative phosphorylation with minimal generation of reactive oxygen species (Birk et al., 2013; Szeto, 2014). Compared to SS-31, SBT-272 shows higher mitochondrial uptake, greater concentrations in the brain, and higher bioavailability (StealthBT.com). SBT-272 is currently in a phase 1 trial in healthy subjects (BioSpace.com).

Neuroprotective Benefit: SBT-272 shows significantly higher brain accumulation than SS-31 in rodent studies. SBT-272 has shown neuroprotective benefits in +rodent models of ALS, Parkinson's, and ischemic stroke. No data on cognitive benefits exist to date.

Types of evidence:

- 0 clinical trials
- Several 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: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
SBT-272 has been examined in rodent models of cerebral ischemia, Parkinson's disease, and ALS.

In a study in normal rats, subcutaneous administration of SBT-272 produced significantly higher brain accumulation compared to SS-31 (elamipretide)(Gautam et al., 2020 poster).

In rats given an ischemic stroke (MCAO model), administration of endothelin-1 vasoconstrictive peptide reduced the mitochondrial respiratory control ratio, but SBT-272 treatment preserved mitochondrial respiration in brain homogenates to levels comparable to sham control (Gautam et al., 2020 poster).

Misfolded or mutated alpha-synuclein is associated with Parkinson's disease and other neurodegenerative diseases. (Bido et al., 2021 poster). In a mouse model of Parkinson's disease (mice injected with mutated human alpha-synuclein A53T bilaterally into the substantia nigra), SBT-272 treatment (0.5 and 5 mg/kg/day, i.p.) partly prevented the loss of dopaminergic neurons and decreased alpha-synuclein burden in the substantia nigra. At the higher dose (5 mg/kg/day, i.p.), microglial (Iba-1) and astrocytic (GFAP) markers were also reduced, suggesting lower neuroinflammation.

Mutations in the superoxide dismutase (SOD1), an antioxidant enzyme, are responsible for about 20% of familial ALS cases. In a mouse model of ALS with an SOD1 mutation (SOD1 G93A transgenic mice), treatment with SBT-272 delayed neurological symptom onset, though outcomes depended on dose and sex (Keefe et al., 2019 poster). Two intraperitoneal doses were tested: 0.5 and 5.0 mg/kg/day. Treatment started at the age of 8 weeks old and continued for 10 weeks or until death for the survival

analysis. In male G93A mice, high dose SBT-272 (5.0 mg/kg/day) delayed the progression of neurological symptom onset relative to vehicle-treated mice. This effect was not seen in female SOD1 G93A mice, which present with a milder disease phenotype (lower neurological symptom score).

Also in male SOD1 G93A mice, high dose SBT-272 treatment (5.0 mg/kg/day) significantly increased lifespan compared to the vehicle control (Keefe et al., 2019 poster). There were no effects on lifespan in female SOD1 G93A mice, consistent with the milder disease phenotype and relatively longer survival compared to male counterparts.

SBT-272 treatment failed to statistically improve grip strength in SOD1 G93A mice. However, in male SOD1 G93A mice, a high dose treatment with SBT-272 (5.0 mg/kg/day) demonstrated a trend in protection from loss of grip strength (p=0.08) (Keefe et al., 2019 poster). No such trend was present in female SOD1 G93A mice.

Plasma levels of neurofilament light chain (NfL), a marker of axonal damage, was significantly reduced in male SOD1 G93A mice treated with high dose SBT-272 (5.0 mg/kg/day) for 10 weeks (Keefe et al., 2019 poster). No treatment effects were seen in female SOD1 G93A mice; NfL levels were overall lower than males, with or without treatment, consistent with the milder disease phenotype in female G93A mice. Plasma NfL levels were significantly correlated with survival, such that higher NfL levels were associated with shorter lifespan.

TDP-43 pathology is observed in more than 90% of ALS patients and in a subset of frontotemporal dementia patients, Lewy body dementia, progressive supranuclear palsy, and Alzheimer's patients. In corticospinal motor neurons exposed to TDP-43 pathology, SBT-272 treatment improved neuronal health as measured by average axonal length (Gautam et al., 2020 poster).

APOE4 interactions: Unknown.

Aging and related health concerns: No studies with SBT-272 have been carried out for age-related diseases.

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

It is not known whether SBT-272 prevents or improves symptoms of age-related diseases, as no such studies have been carried out in laboratory or clinical studies.

Safety: No safety or toxicology studies have been published to date. In a mouse model of ALS, SBT-272 extended lifespan, suggesting long-term treatment in mice is likely safe. Chronic toxicology studies and a phase I clinical study are underway.

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

No publications on safety or toxicology data for SBT-272 are available to date. A dose-ranging phase 1 clinical study as well as chronic toxicology studies are underway (PRnewswire.com).

In male SOD1 G93A mice, high dose SBT-272 treatment (5.0 mg/kg/day) started at 8 weeks of age and continued until end of life significantly increased lifespan compared to the vehicle-treated mice (Keefe et al., 2019 poster). Treatment lasted up to 14 weeks.

Drug interactions: Drug interactions with SBT-272 have not been documented.

Sources and dosing: SBT-272 is under development by Stealth BioTherapeutics Inc for the treatment of ALS and MSA. Dosing has not been established for humans. In rodents, SBT-272 has been tested at doses of 0.5 and 5.0 mg/kg/day, i.p. (or s.c.).

Research underway: In January 2020, Stealth BioTherapeutics Inc. initiated a first-in-human phase 1 study of SBT-272 in 40 healthy subjects (BioSpace.com). It is a double-blind, placebo-controlled, single-ascending dose study that will evaluate safety and tolerability of SBT-272 administered orally. Secondary objectives include pharmacokinetic profiling and dose-finding.

Search terms: SBT-272

Websites visited for SBT-272:

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