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.

TQS-168

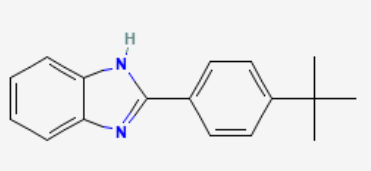
Evidence Summary

No clinical trials have been completed in neurodegenerative or age-related diseases. A phase 1 trial has been completed, but detailed results have not been published.

Neuroprotective Benefit: PGC-1α mRNA and protein expression is decreased as a function of clinical severity of dementia. No clinical trials to date have tested TQS-168 for the treatment of dementia or prevention of age-related cognitive decline.

Aging and related health concerns: Rodent studies suggest potential benefits of TQS-168 in models of cardiomyopathy, diabetes, kidney disease, and lung disease. Its role in promoting/suppressing cancer is unclear. No clinical data in humans exist to date.

Safety: A phase I study reported that adverse events with TQS-168 were mild and transient, with no serious adverse events. However, detailed results have not been published in a peer-reviewed journal.

Availability: in clinical development	**Dose**: not established	**Chemical formula:** $C_{17}H_{18}N_2$ **MW**: 250.34  Source: PubChem
Half-life: not published	**BBB**: penetrant	
Clinical trials: A phase I clinical trial has tested TQS-168 in 78 healthy volunteers.	**Observational studies**: none available	

What is it?

TQS-168 (also known as ZLN005) is a blood-brain barrier penetrant novel small molecule that modulates peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α. PGC-1α is a transcription regulator that coactivates transcription factors such as peroxisome proliferator-activated receptor (PPARs, e.g., PPARα, PPARδ/β, and PPARγ), nuclear respiratory factors 1 and 2 (NRF-1 and 2), estrogen receptors, thyroid hormone, glucocorticoid, and others (reviewed in Miller et al., 2019; Mota et al., 2021). PGC-1α plays a role in mitochondrial biogenesis and regulation of cellular energy metabolism, including gluconeogenesis, glucose transport, fatty acid oxidation, and adaptive thermogenesis involving brown adipocytes. PGC-1α can be induced by cold, fasting, and physical exercise. Alterations in PGC-1α levels have been associated with metabolic disorders such as type 2 diabetes mellitus, obesity, cardiovascular disease, and hepatic steatosis (reviewed in Liang and Ward, 2006; Mota et al., 2021; Cheng et al., 2018).

TQS-168 is under development by the Tranquis Therapeutics Inc., a clinical-stage biopharmaceutical company, for the treatment of amyotrophic lateral sclerosis (ALS)(Tranquis pipeline page). The company's approach is to reprogram dysfunctional myeloid immune cells to restore normal cell homeostasis and function. Exploratory development of TQS-168 is also ongoing for other orphan indications including frontotemporal dementia, Huntington's disease, muscular dystrophy, and Friedreich's ataxia. In June 2022, the US FDA granted Tranquis Therapeutics Inc. orphan drug designation for TQS-168 for the treatment of ALS (ALS News Today, June 24, 2022).

Neuroprotective Benefit: PGC-1α mRNA and protein expression is decreased as a function of clinical severity of dementia. No clinical trials to date have tested TQS-168 for the treatment of dementia or prevention of age-related cognitive decline.

Types of evidence:

- One phase I study in healthy volunteers
- Several observational studies on PGC-1α expression in Alzheimer's disease
- Several laboratory studies

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

No clinical trials to date have tested TQS-168 for the prevention of dementia or age-related cognitive decline.

Human research to suggest benefits to patients with dementia:

No clinical trials to date have tested TQS-168 in patients with dementia.

In a postmortem analysis, PGC-1α mRNA and protein expression in the Alzheimer disease brain decreased as a function of clinical severity of dementia, measured by the Clinical Dementia Rating (Qin et al., 2009). PGC-1α protein content inversely correlated with neuritic plaque pathology and Aβ42 contents.

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

Phase 1 clinical trial: In June 2022, Tranquis Therapeutics Inc. announced the completion of its phase I clinical trial of TQS-168 (Tranquis press release, 6/2/2022). Single and multiple doses of TQS-168 were tested in 78 healthy volunteers, and based on the company, they demonstrated "excellent pharmacokinetic properties and adequate plasma exposures". Details of the results from this phase I study have not been published in a peer-reviewed journal as of January 2024.

Models of Alzheimer's disease: No published studies have tested TQS-168 in models of Alzheimer's disease. However, several preclinical studies support the potential neuroprotective action of stimulating PGC-1α. In a mouse model of Alzheimer's disease (APP23 mice), overexpression of PGC-1α significantly

improved spatial and recognition memory, preserved neurons, and reduced Aβ deposition, which was associated with a decrease in BACE1 expression (Katsouri et al., 2016). PGC-1α overexpression also decreased the levels of proinflammatory cytokines (TNF-α, IL-1β) and microglial activation (IBA1), and increased levels of the neurotrophic factor, BDNF. In embryonic cortico-hippocampal neurons derived from a mouse model of Alzheimer's disease (Tg2576 mice), under hyperglycemic conditions, the decrease in PGC-1α expression coincided with the elevation of Aβ42 and Aβ40 accumulation (Qin et al., 2009). In neurons from Tg2576 mice, increasing PGC-1α expression attenuated the hyperglycemic-mediated amyloidogenesis through the attenuation of the expression of forkheadlike transcription factor 1 (FoxO3a).

Models of ALS: Findings from a study in a mouse model of ALS were presented during the 2021 Society for Neuroscience annual meeting. In a mouse model of ALS (SOD1-G93A mice), TQS-168 treatment (50 mg/kg, 3 times per week) reduced "inflammatory monocytes and inflammation-promoting signaling molecules" (ALS News Today, 11/12/2021). TQS-168-treated SOD1-G93A mice also lived 6 days longer than those left untreated (135 days versus 129 days). When various amounts of TQS-168 were mixed with blood samples from patients with ALS for 4 hours, TQS-168 decreased the percentage of inflammatory monocytes, which are usually increased in people with ALS. Details of this study have not been published in a peer-reviewed journal as of January 2024.

Model of ischemic stroke: In a rat model of ischemic stroke (transient middle cerebral artery occlusion), treatment with ZLN005 (2.5 mg/kg, i.v.) 2, 4, or 6 hours after ischemia onset significantly reduced infarct volume, improved neurological deficit, and enhanced the expression of PGC-1α in the ipsilateral brain hemisphere of the occlusion (Xu et al., 2018). When ZLN005 was administered 2 or 4 hours post-ischemia, infarct volume was reduced by ~75%. When ZLN005 was administered 6 hours post-ischemia, infarct volume was reduced by ~50%. In a cell culture model of ischemia (PC12 cells subjected to oxygen-glucose deprivation, then reoxygenation), ZLN005 administration reduced cell injury, while enhancing the expression of PGC-1α, antioxidant genes (SOD1 and HO-1), and prevented the ischemia-induced decrease in SOD activity.

APOE4 interactions:

Unknown.

Aging and related health concerns: studies suggest potential benefits of TQS-168 in models of cardiomyopathy, diabetes, kidney disease, and lung disease. Its role in promoting/suppressing cancer is unclear. No clinical data in humans exist to date.

Types of evidence:

- Numerous laboratory studies

Cardiovascular disease: POTENTIAL BENEFIT BASED ON RODENT STUDIES
Cardiomyopathy, particularly dilated cardiomyopathy, contributes to the development and progression of heart failure. In a mouse model of dilated cardiomyopathy (induced by doxorubicin), ZLN005 treatment (4 doses of 2.5 mg/kg, i.v.) 2 hours after doxorubicin then every alternate day significantly attenuated fibrosis, and alleviated the increases in necroptosis markers (RIPK1, RIPK3, MLKL) and oxidative stress biomarkers (decreased 8-OHdG, malondialdehyde, and increased GSH:GSSG ratio, catalase, SOD, glutathione, glutathione reductase)(Shipra et al., 2023).

Mitochondrial deficits have been suggested as one of the contributing factors to the development of heart failure. In a mouse model of heart failure (cardiomyocyte specific-Cse knockout mice given a high-fat diet and I-NAME, an inhibitor of constitutive nitric oxide synthases), ZLN005 treatment (15 mg/kg/day, i.g.) for 4 weeks reduced mitochondrial abnormalities and cardiac diastolic dysfunction, while increasing the expression of PGC-1α and its downstream proteins, NRF1 and TFAM (Huang et al., 2023).

Cancer: MIXED; POTENTIAL HARM BASED ON A CELL CULTURE STUDY
PGC-1α has been shown to regulate cancer metabolism, though its role is mixed and complex; it appears to have a biphasic role, acting both as a tumor suppressor and a tumor promoter (reviewed in Cheng et al., 2018).

PGC-1α is highly expressed in prostate cancer PC3 and DU145 cells with p53 deletion or mutation. These mutations often damage the function of p53 protein and are associated with tumor progression in prostate cancer patients (Ecke et al., 2010). Overexpression of p53 in prostate cancer PC3 cells resulted in inhibition of protein expression and nuclear localization of PGC-1α, inhibition of genes and proteins associated with mitochondrial biogenesis and fission/fusion, mitochondrial dysfunction, and cancer cell apoptosis (Li et al., 2020). In contrast, activation of PGC-1α by ZLN005 partially reversed the p53-mediated mitochondrial dysfunction. Thus, in this study, PGC-1α activation was associated with a pro-cancer effect.

Diabetes: POTENTIAL BENEFIT BASED ON RODENT STUDIES

In a mouse model of type 2 diabetes (diabetic db/db mice), ZLN005 treatment for 6 weeks increased PGC-1α expression and downstream gene transcription including GLUT4, mitochondrial oxidative phosphorylation genes (e.g., ERRα, cytochrome-c, cox5b, ATPase-F1α, and uncoupling protein 3), and fatty acid oxidation genes (medium-chain acyl-CoA dehydrogenase and long-chain acyl-CoA dehydrogenase) in the gastrocnemius skeletal muscle (Zhang et al., 2013). Also in the gastrocnemius of db/db mice, ZLN005 treatment increased mitochondrial DNA by 31%. In contrast, in the liver of db/db mice, PGC-1α was reduced by 34%, and its downstream gluconeogenesis genes, glucose-6-phosphatase and PEPCK, were reduced by 31% and 27%, respectively, and no changes in mitochondrial DNA were found. In db/db mice, ZLN005 treatment reduced nonesterified fatty acids, triglyceride, and cholesterol levels by 20%, 37%, and 10%, respectively. ZLN005 treatment also increased fat oxidation, decreased fasting blood glucose levels, and improved glucose tolerance, pyruvate tolerance, and insulin sensitivity in db/db mice. ZLN005 treatment did not alter glucose tolerance, lipid measures, or insulin sensitivity in lean mice. ZLN005 treatment did not affect body weight gain or food intake in either db/db mice or lean mice. Pharmacokinetic studies in db/db mice showed that a single oral ZLN005 dose of 15 mg/kg was absorbed into the plasma quickly, reaching a concentration of 3.7 µmol/L within 15 min, and a decline in concentration to 0.44 µmol/L within 4 hours. The concentration of ZLN005 in muscle tissue was stable at approximately 3-4 µmol/L over 4 hours. Based on some observed tissue-specific changes in gene expression and downstream effects, ZLN005 treatment may have tissue-specific effects..

Diabetic cardiomyopathy increases the risk for the development of heart failure. Hyperglycemia can induce apoptotic cell death in mouse myocardium (Cai et al., 2002). In neonatal mouse cardiomyocytes incubated with high levels of glucose, ZLN005 treatment ameliorated cardiomyocyte oxidative stress, enhanced cell viability, and reduced apoptosis (Li et al., 2016). ZLN005 treatment also increased protein levels of autophagy markers (ATG5, beclin1, and LC3 II/LC3 I) as well as expression of SIRT1 (mRNA and protein; involved in metabolic responses).

Kidney disease: POTENTIAL BENEFIT BASED ON RODENT STUDIES

Chronic kidney disease is a condition in which kidneys are damaged and cannot filter blood properly, resulting in excess fluid and waste from blood building up, which may cause other health problems such as heart disease and stroke. In a mouse model of chronic kidney disease (mice with unilateral ureteral obstruction surgery), ZLN005 pretreatment (prior to surgery; 40 mg/kg, i.g.) showed reduced kidney damage and expression of fibrotic biomarkers than control mice (Zhu et al., 2022). ZLN005 treatment inhibited the unilateral ureteral obstruction surgery-induced renal inflammation, measured by IL-1β, IL-

6, TNF-α, and iNOS. ZLN005 treatment on renal damage and fibrosis had a magnitude of effect as large as that of fenofibrate. Also, in a cell culture model of chronic kidney disease (TGF-β1-treated renal tubular epithelial cells), ZLN005 treatment alleviated the fibrotic phenotype and lipid accumulation. ZLN005 treatment improved mitochondrial homeostasis, in part, by the activation of PGC-1α, thus maintaining mitochondria function and energy homeostasis.

Ischemia-reperfusion injury due to low blood flow or sepsis is a common cause of acute kidney injury. In a mouse model of acute kidney injury (induced by ischemia-reperfusion), ZLN005 treatment (3, 6, or 12 mg/kg, i.p.) alleviated the ischemia-reperfusion-induced tubular injury (Wang et al., 2021). In a cell culture model of hypoxia-reoxygenation, ZLN005 treatment inhibited the drop in cell viability by restoring PGC-1α expression in a dose-dependent manner. The protective effect of ZLN005 was through the restoration of mitochondrial fatty acid oxidation and mitigation of endoplasmic reticulum stress.

In a different mouse model of acute kidney injury (induced by cisplatin), PGC-1α expression was decreased, but ZLN005 treatment (15 mg/kg/day, i.g., same time as cisplatin injection) for 4 days alleviated kidney injury, restored PGC-1α expression, and decreased levels of blood urea nitrogen (BUN) and creatinine, markers of kidney disease (Yuan et al., 2021). In cell culture, overexpression of PGC-1α or ZLN005 treatment inhibited cell apoptosis and mitochondrial dysfunction induced by cisplatin. ZLN005 treatment also activated mitophagy, measured by the increased expression of LC3-II and co-localization of LC3 and mitochondria, and autophagy, measured by the increased expression of TFEB.

Lung disease: POTENTIAL BENEFIT BASED ON PRECLINICAL STUDIES
Idiopathic pulmonary fibrosis is a chronic and fatal pulmonary disease that usually occurs in the elderly. In lung tissues of idiopathic pulmonary fibrosis patients, expressions of PGC-1α and NRF-1 (involved in mitochondrial synthesis) were decreased (Ma et al., 2023). PGC-1α and NRF-1 expressions were also decreased in a mouse model of pulmonary fibrosis (bleomycin-induced) as well as in a model of cell senescence (A549 cells treated with hydrogen peroxide). Treatment with ZLN005 inhibited the hydrogen peroxide-induced cell senescence by enhancing the expression of PGC-1α and improving mitochondrial function.

Safety: A phase I study reported that adverse events with TQS-168 were mild and transient, with no serious adverse events. However, detailed results have not been published in a peer-reviewed journal.

Types of evidence:

- One phase I study in healthy volunteers
- Several laboratory studies

Clinical trial data: In a phase I clinical trial of TQS-168, single and multiple doses of TQS-168 were tested in 78 healthy volunteers (Tranquis press release, 6/2/2022). Details of the results from this phase I study have not been published in a peer-reviewed journal as of January 2024. Based on the Tranquis Therapeutics's press release, "no serious adverse events were reported" and adverse events were "mild, transient, and did not lead to treatment discontinuation".

Preclinical data: In rats, ZLN005 treatment (75 mg/kg/day) orally for 14 days did not result in obvious changes in body weight gain or metabolic parameters, and all animals survived (Zhang et al., 2013). Although ZLN005 treatment significantly reduced fasting blood glucose levels in a mouse model of diabetes (db/db mice), no changes in plasma glucose were seen in lean mice.

In neonatal mouse cardiomyocytes under normal glucose conditions, ZLN005 treatment increased SIRT1 expression and increased cell apoptosis (Li et al., 2016). ZLN005 treatment increased cell apoptotic rates to 2.88 ± 0.16% compared to 2.31 ± 0.14% in untreated controls ($p<0.05$). Further studies are needed to fully understand the effects, including possible cytotoxic effects, of ZLN005 on the heart and on the rest of the body under normal and high glucose conditions.

Drug interactions: Drug interactions have not been documented.

Sources and dosing:

TQS-168 is under development by the Tranquis Therapeutics Inc., a clinical-stage biopharmaceutical company (Tranquis pipeline page). A phase I clinical trial testing single and multiple doses of TQS-168 was completed in 2022 (Tranquis press release, 6/2/2022). However, details of the doses tested and the results from this phase I study have not been published in a peer-reviewed journal as of January 2024.

Research underway:

As of January 2024, there are no ongoing clinical trials testing TQS-168, based on ClinicalTrials.gov. Based on Tranquis Therapeutics' company website, TQS-168 is under clinical development for ALS, frontotemporal dementia, Huntington's disease, muscular dystrophy, Friedreich's ataxia, and other indications (Tranquis pipeline page).

Search terms:
Pubmed, Google: TQS-168, ZLN005

Websites visited for TQS-168, ZLN005:

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