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.

FGF21 Analogs

Evidence Summary

FGF21 analogs appear to have benefit for MASH and hypertriglyceridemia; phase 3 trials are ongoing. Effects on bone health, as well as effects of long-term use, are not yet known.

Neuroprotective Benefit: Some preclinical data suggest that FGF21 could be neuroprotective, but this data is preliminary. There is no clinical data suggesting that treatment with FGF21 or analogs can improve neurological conditions including AD.

Aging and related health concerns: Clinical trials suggest that FGF21 analogs may become treatment options for MASLD/MASH and hypertriglyceridemia; more trials are ongoing.

Safety: Clinical data currently indicates gastrointestinal complaints are the most common side effect; most are mild to moderate in nature. Effects on bone health, as well as effects from long-term use, must be explored.

Availability: In clinical development	**Dose**: Not known yet; FGF21 analogs in development are administered via subcutaneous injection.	**Wildtype FGF21** **Chemical formula:** N/A **MW:** ~19 kDa
Half-life: Native FGF21, 0.5-2 hours; half-life of analogs varies	**BBB**: Native FGF21 appears to cross the BBB; it is not yet known whether each individual FGF21 analog is BBB penetrant.	
Clinical trials: Several trials of different FGF21 analogs have been completed; the largest meta-analysis of RCTs included 1,054 participants.	**Observational studies**: No observational studies have examined the use of exogenous FGF21 or FGF21 analogs.	

What is it?

Fibroblast growth factors (FGF) are a set of twenty-two proteins that are critically involved in many cellular functions. Most are autocrine and paracrine factors that bind to one or some of the four FGF receptors (FGFR). FGF21, along with FGF19 and FGF23, are unique among the FGFs in that they can be secreted and thus act in an endocrine fashion. These endocrine FGFs are important for whole-body homeostasis, including regulating bile acid, glucose and lipid metabolism, modulating vitamin D and phosphate homeostasis, and they induce metabolic adaptation in response to fasting (Degiroamo et al., 2015). FGF21 is released by the liver and then binds to a heterodimer of β-Klotho in a complex with an FGFR isomer to exert its effects on glucose and lipid metabolism, adiposity, and insulin regulation (Geng et al., 2020). When an organism has an energy deficit, FGF21 supports survival by increasing ketogenesis and fuel utilization through mitochondrial fatty acid oxidation (Xie & Leung, 2017). In addition to its metabolic effect, FGF21 is reported to be involved in the browning of white adipose tissue, stimulation of the hypothalamic-pituitary-adrenal axis, and the regulation of circadian rhythm during fasting. FGF21 levels show a correlation with the circadian rhythm, increasing at midnight, peaking in the early morning, and decreasing in the early afternoon (Degiroamo et al., 2015). FGF21 levels vary widely

(Galman et al., 2008). They may also be increased by exposure to cold temperatures in thermogenic adipose tissue (Degiroamo et al., 2015).

Determining the beneficial/detrimental effects of FGF21 by circulating levels is difficult, as patients with obesity, T2DM, NAFLD, coronary heart disease (CAD), and other metabolic syndromes have increased levels of circulating FGF21. This apparent paradox – beneficial metabolic effects of exogenous FGF21 but increased levels in disease – could be due to FGF21 resistance (similar to insulin resistance) in patients with metabolic syndrome. In fact, obese mice have reduced expression of FGFR1 and β-Klotho (Xie & Leung, 2017).

Another complication is that some rodent data conflicts with primate and human data. For instance, while rodents lose weight despite eating the same amount after FGF21 treatment, weight loss in non-human primates is primarily due to less food consumption. Similarly, while FGF21 reduces glucose levels in rodents, the glucose-lowering effect in humans is not as significant (Sonoda et al., 2017).

Recombinant FGF21 has a short half-life, so the development of therapeutics for humans has focused on FGF21 mimetics that stay in circulation longer. Several of these FGF21 analogs have been or are currently in clinical trials for metabolic diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), and hypertriglyceridemia (Cui et al., 2024). Other groups are exploring the utility of FGFR agonists or combination therapies of FGF21 analogs with other drugs such as GLP-1 receptor agonists; these approaches are not in the scope of this report but demonstrate the growing interest in treatment approaches in the FGF21 pathway.

A note on nomenclature in this report: until 2023, fat accumulation in the liver in individuals who do not consume alcohol was known as nonalcoholic fatty liver disease (NAFLD). Nonalcoholic steatohepatitis (NASH) was the term used for a severe form of NAFLD; in NASH, there is also inflammation and liver damage in addition to fat accumulation. In 2023, an international group of experts voted to replace the term NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD) and NASH with metabolic dysfunction-associated steatohepatitis (MASH) (American Association for the Study of Liver Disease). This report will use MASLD / MASH, but it should be noted that any trial that was registered or paper published before the name change will refer to these conditions as NAFLD or NASH.

Neuroprotective Benefit: Some preclinical data suggest that FGF21 could be neuroprotective, but this data is preliminary. There is no clinical data suggesting that treatment with FGF21 or analogs can improve neurological conditions including AD.

Types of evidence:

- 4 reviews
- 1 commentary
- 1 study suggesting FGF21 can cross the blood brain barrier in mice
- 5 preclinical studies suggesting FGF21 may be neuroprotective

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

FGF21 and/or its analogs have not been explored for cognitive effects or for dementia prevention in humans. Clinical trials have reported potential benefits of FGF21 analogs for dyslipidemia. If these effects prove to be robust and lead to significant cardiovascular benefit, then this could indirectly lead to lower dementia risk via improved cardiovascular health. However, this remains a theoretical hypothesis.

Human research to suggest benefits to patients with dementia:

There are no studies of FGF21 or its analogs in patients with dementia.

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

Whether FGF21 and/or its analogs have clinically relevant neuroprotective actions is not yet known. There are several potential mechanisms through which FGF21 and/or analogs could mitigate insults to or improve brain health. First, there is a possible indirect route of neuroprotection. FGF21 analogs appear to reduce dyslipidemia. There is controversy in the field as to whether dyslipidemia is a risk factor for dementia, but if it is, treating the risk factor could theoretically help prevent dementia as well (Iwagami et al., 2021; commentary by Ishii, 2021). FGF21 or its analogs may also mediate neuroprotective action more directly.

As reviewed by Yang & Nao, 2023, FGF21 is thought to have anti-inflammatory, antioxidant, and pro-survival actions in neurons, and may modulate autophagy. Modulating lipid or glucose homeostasis

could have beneficial effects in the brain. FGF21 administration has also been shown to reduce tau hyperphosphorylation and Aβ plaque load in animal models. These effects have been seen in animal models of both AD and Parkinson's Disease (PD), with FGF21 promoting synaptic plasticity, reducing inflammation and oxidative stress, and mitigating neurodegeneration and cognitive decline in a number of studies.

In vitro studies suggest that FGF21 increases the expression of peroxisome proliferator activated receptor g coactivator 1α (PGC-1α – a transcriptional coactivated important for mitochondrial biogenesis), increased the expression of SIRT1, increased the NAD/NADH ratio, and enhanced the mitochondrial respiratory capacity in human dopaminergic neurons (Makela et al., 2014). These results are reflected in another *in vitro* study where human brain vascular smooth muscle cells (hBVSMCs) were exposed to Ang II to induce an aging phenotype (increased expression of β-gal staining, p53, and reduced complex IV activity). Coadministration with FGF21 attenuated the Ang II-induced aging phenotype. FGF21 was thought to act through AMPK activation, as coadministration with an AMPK inhibitor abolished the beneficial FGF21 effects (Wang et al., 2016). In human neuroblastoma cells, FGF21 improved survival after Aβ-induced toxicity (interestingly it was most effective at the lowest doses), reduced ROS generation, reduced caspase 3 activity (a marker of apoptosis), and reduced expression of NF-kβ (Amiri et al., 2018).

In a mouse model of toxin-induced demyelination, FGF21-KO mice had increased demyelination and there was a decrease in oligodendrocyte precursor cell (OPC) proliferation when β-Klotho was knocked out of OPC cells, suggesting that peripheral FGF21 is important to remyelination. Additionally, the same group found that β-Klotho expression was increased in the spinal cord of patient with MS (Kuroda et al., 2017).

In a mouse model of aging where D-galactose was administered with or without FGF21 for 8 weeks, animals administered FGF21 had improved cognition, reduced hippocampal neuron loss, reduced levels of ROS, advanced glycation endproducts, markers of lipid peroxidation, pro-inflammatory cytokines, and reduced expression of NF-kB. Additionally, treated animals had increased expression of antioxidant enzymes SOD and catalase (Yu et al., 2015). Long-term caloric restriction was also reported to increase FGF21 brain and plasma levels, FGFR downstream signaling, and reduce mTOR phosphorylation. However, whether these effects were due to FGF21 or some other effects of caloric restriction were not investigated (Ruhlmann et al., 2016).

Labeled FGF21 was reported to enter the brain of mice 10 minutes after intravenous bolus injection (Hsuchou et al., 2007). Additionally, FGF21 was reported to be in human CSF at 40% of levels found in plasma, suggesting it is either produced locally or can cross the blood brain barrier (Tan et al., 2011). Which, if any, of the FGF21 analogs can cross the blood-brain barrier remains to be seen.

It is not clear which, if any, of these mechanisms may be at play in humans. FGF21 exerts its actions through binding to a receptor complex containing an FGFR and β-klotho. Available data suggest that β-klotho is expressed at high levels in mouse brain but not in human brain. FGF21 modulates thermogenesis in brown adipose tissue (BAT) in mice, which may underpin its effects on rodent body weight or glucose homeostasis, but rodents have significantly more BAT than humans. There is also data to suggest that there can be resistance to FGF21 in humans. It is unclear, too, how FGF21 analogs may (or may not) have different effects than native FGF21 (reviewed in Yang & Nao, 2023). More work is needed to clarify whether FGF21 analogs have meaningful neuroprotective effects in humans.

APOE4 interactions:

It is not yet known whether FGF21 or its analogs have different effects based on APOE4 status.

Aging and related health concerns: Clinical trials suggest that FGF21 analogs may become treatment options for MASLD/MASH and hypertriglyceridemia; more trials are ongoing.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 9 clinical studies on FGF21 mimetics for metabolic disease
- 1 observational study
- 3 reviews
- 4 laboratory studies

Metabolic dysfunction-associated steatohepatitis (MASH): LIKELY BENEFIT

Several trials have or are exploring the use of FGF21 analogs in MASH (previously known as NASH). A 2024 meta-analysis of nine RCTs with 1,054 patients with MASH found that FGF21 analogs (efruxifermin, pegozafermin, and pegbelfermin) significantly improved fibrosis without worsening MASH (RR=1.79;

95% CI 1.29 to 2.48, p<0.001). This study did not find a statistically significant improvement in MASH without worsening of fibrosis in FGF21 analogs compared to placebo. However, when the authors performed sensitivity analyses and excluded the study of pegbelfermin, they found that there was a statistically significant improvement in MASH without fibrosis. Work on pegbelfermin has been discontinued. In secondary analyses, the authors found that FGF21 analogs improved several liver indices, such as hepatic fat fraction and liver enzymes (Lin et al., 2024).

Another meta-analysis, this one including eight RCTs with a total of 963 patients with MASH, also found that FGF21 analogs significantly improved fibrosis without worsening of MASH (RR=1.83; 95% CI 1.27 to 2.62) and improvement on the non-alcoholic fatty liver disease activity score without worsening of fibrosis (RR=2.85; 95% CI 2.06 to 3.95). This study also found improvements in many liver indices and found that FGF21 analogs did not significantly improve MASH with no worsening of fibrosis. The authors also reported that FGF21 analog treatment improved adiponectin levels compared to placebo. The authors compared the treatments and found pegbelfermin to be the least effective (Jeong et al., 2024).

There are several ongoing Phase 3 trials of FGF21 analogs in MASH; more details can be found in the 'Research Underway' section.

Dyslipidemia: LIKELY BENEFIT

A 2024 meta-analysis assessed the performance of FGF21 analogs compared to placebo in patients with MASH. The meta-analysis included a total of nine trials, but not all looked at changes in lipid levels. The authors reported significant improvements in triglyceride levels (2 trials, p=0.006), HDL-c (3 trials, p<0.001) and LDL-c levels (3 trials, p=0.002) in the studies that assessed lipid changes (Lin et al., 2024).

Given these positive results in patients with MASH, researchers have also assessed FGF21 analogs in patients with severe hypertriglyceridemia. ENTRIGUE was a blinded RCT of placebo or different doses of pegozafermin (9 mg once weekly; 18 mg once weekly; 27 mg once weekly; 36 mg every other week) in 85 patients with severe hypertriglyceridemia. Dosing lasted for 8 weeks. Patients treated with pegozafermin had significantly reduced triglyceride levels after 8 weeks, regardless of dose. When authors pooled the pegozafermin data together, the placebo-corrected median percent change in triglycerides was -43.7% (−57.3% versus −11.9% placebo; 95% CI −57.1% to −30.3%; p< 0.001). Of the participants, 29% of the placebo group achieved a target triglyceride level of <500 mg/dL; 79.7% of all the participants receiving pegozafermin achieved that triglyceride normalization. Pegozafermin

treatment also led to improvements in non-HDL-c and hepatic fat fraction. The 27 mg weekly dose appeared to have the most benefit (Bhatt et al., 2023).

A 12-week blinded RCT of LLF580, now named BOS-580, in 62 participants with obesity and modest hypertriglyceridemia, treatment with this FGF21 analog was associated with a -54% change in triglycerides compared to placebo. Improvements in total cholesterol, LDL-c, and HDL-c were also observed, as were improved liver function tests and a -52% change in liver fat compared to placebo (Rader et al., 2022).

Pfizer tested an FGF21 formulation (PF-05231023) with an increased half-life in obese individuals with or without T2DM for 28 days at doses ranging from 5-150 mg once or twice per week. At higher doses, PF-05231023 improved lipid profiles (triglycerides ~-50%, LDL-c ~-20%, HDL-c ~+20%), and increased adiponectin (~1500%) (Talukdar et al, 2016; Dong et al, 2015; Kim et al, 2017).

An RCT with another FGF21 mimetic (LY2405319) reported similar results in obese patients with T2DM over 28 days. LY2405319 reduced LDL-c and ApoB (~25%), increased HDL-c (~17%), reduced ApoC3 (~35%), reduced triglycerides (~45%), did not change glucose levels, reduced fasting insulin (~35%), increased adiponectin (~5500%), increased beta-hydroxybutyrate (~1%), and decreased weight (~1.5%). There were no serious adverse events (Gaich et al., 2013).

Diabetes and Obesity: DOES NOT APPEAR TO HAVE BENEFIT

Despite promising preclinical data, the bulk of the clinical studies thus far have not shown that most FGF21 analogs improve glycemic control or significantly benefit weight management (two studies meta-analyzed by Lin et al., 2024; reviewed in Chui et al., 2024; includes 13 clinical studies).

This may depend on the specific FGF21 analog, as each analog has a different half-life, dosing regimen, and binding affinity to different FGFRs, or on whether the FGF21 analog is used in combination with another drug. For instance, one randomized controlled study of efruxifermin in 31 patients with MASH and type 2 diabetes (T2D) who were already receiving GLP-1 receptor agonist (GLP-1 RA) treatment reported greater weight loss and glycemic control in the patients receiving efruxifermin and GLP-1 RAs than patients receiving GLP-1 RAs and placebo (Harrison et al., 2024). As this is a small trial and a combination therapy, future work is needed to fully explore the potential effects of each FGF21 analog

on glycemic control and body weight in humans to determine if or under what circumstances FGF21 analogs may have benefit.

Pfizer tested an FGF21 formulation (PF-05231023) with an increased half-life in obese individuals with or without T2DM for 28 days at doses ranging from 5-150 mg once or twice per week. There were no changes in insulin resistance or glucose control. (Talukdar et al., 2016; Dong et al., 2015; Kim et al., 2017).

An RCT with another FGF21 mimetic (LY2405319) reported similar results in obese patients with T2DM over 28 days. LY2405319 did not change glucose levels but did reduce fasting insulin (~35%) (Gaich et al., 2013).

Lifespan: NOT KNOWN IF THERE IS BENEFIT OR NOT

Zhang et al., 2012 reported that mice that overexpress FGF21 in hepatocytes (to levels 5-10x seen during prolonged fasting) live 36% longer than control mice (with more benefits in females than males; in fact, at 44 months, >30% of the females were still alive). FGF21 mice weighed less but had similar levels of food consumption, physical activity, and oxygen consumption as control mice. FGF21 mice had higher levels of ketone, lower triglycerides (in females), lower IGF-1, and increased insulin sensitivity, but also decreased bone mass. These effects were independent of AMPK, mTOR, and sirtuin pathways (contrary to some other studies). Bone-loss was also seen in younger mice treated with FGF21 for 2 weeks. These effects were thought to be mediated by PPARγ, as FGF21 knockout prevented rosiglitazone-induced bone loss (Wei et al., 2012).

In another study, despite the fact that expression of *Fgfr1* and β-*Klotho* mRNA increased in mice with age in thymic stromal cells, expression of *Fgf21* mRNA decreased, an effect that was reversed with caloric restriction. In addition, although FGF21 overexpressing mice (with 50-100x more circulating FGF21) had decreased body weight, size, and thymic size – when adjusting for body weight these mice had increased relative thymic size, improved thymic morphology, decreased white adipose tissue, and increased brown adipose tissue, suggesting that FGF21 overexpression reduced thymic involution with age. FGF21 also improved the thymic microenvironment and increased T-cell diversity. Opposite effects were seen in FGF21 knockout mice (Youm et al., 2015).

In theory, FGF21 may be a pro-longevity hormone as it acts through many aging-related pathways. Administration of FGF21 to adipocytes *in vitro* enhanced AMPK-SIRT1-PGC1α signaling and mitochondrial oxidative capacity (Chau et al., 2010). FGF21 may also mediate the lifespan extension and metabolic benefits of protein restriction in male mice (Hill et al., 2022). However, it is not yet known whether this translates to meaningful effects in humans, especially given the differences between rodents and humans in terms of receptor expression and adipose tissue composition (Yang & Nao, 2023). Significant work is required to fully understand the effects (or lack thereof) of FGF21 and its analogs on human healthspan.

Safety: Clinical data currently indicates gastrointestinal complaints are the most common side effect; most are mild to moderate in nature. Effects on bone health, as well as effects from long-term use, must be explored.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 5 clinical trials
- 1 review
- 2 preclinical studies

Trials of FGF21 analogs in patients with MASH and hypertriglyceridemia have reported that the most common side effects are gastrointestinal in nature, including nausea and diarrhea. These are typically mild to moderate in nature (Bhatt et al., 2023; Lin et al., 2024). One trial also reported changes in appetite and upper respiratory infections in addition to the gastrointestinal events reported in other studies (Rader et al., 2022). A meta-analysis of nine RCTs of FGF21 analogs (efruxifermin, pegozafermin, and pegbelfermin) compared to placebo found that there were more adverse events reported in the FGF21 analog groups compared to placebo (RR=1.79; 95% CI 1.42 to 2.26, p< 0.001) but that there was no statistically significant difference in serious adverse events (RR=1.26; 95% CI 0.82 to 1.94, p=0.3). Nausea, vomiting, diarrhea, and injection site reaction were the most common adverse events (Lin et al., 2024). Another meta-analysis also found that FGF21 analogs were significantly associated with treatment-related adverse events (RR=1.75; 95% CI 1.40 to 2.19; p<0.00001) and that efruxifermin had the highest instance of treatment-related adverse events, diarrhea, and nausea. The authors found that pegozafermin had the highest incidence of injection site reaction. The authors also reported that despite

these increased risks, FGF21 analog treatment was not associated with increased incidence of serious adverse events or discontinuation due to adverse events (Jeong et al., 2024).

One area of concern is the potential for FGF21 to cause bone loss. FGF21-mediated bone loss is thought to be due to signaling through PPARγ and is thought to be reflected in decreases in bone formation but no changes in bone resorption. FGF21 treatment in mice promotes the differentiation of bone marrow mesenchymal cells into adipocytes rather than osteoclasts (Degirolamo et al., 2016). Future drugs are being developed to target the FGFR1c- β-Klotho receptor complex that could avoid these side effects as β-Klotho has reduced expression in the bone marrow. Some of the early drugs used the FGF21 epitope that could bind to FGFR1 without βklotho, so FGFR1c- β-Klotho receptor complex targeted therapeutics may have a larger therapeutic window.

Preclinical studies suggest that increased FGF21 may induce bone loss, thus increasing the risk of bone fracture (Zhang et al., 2012; Wei et al., 2012). Human studies suggest that FGF21 could change circulating biomarkers of bone turnover (Talukdar et al., 2016; Dong et al., 2015; Kim et al., 2017; Rader et al., 2022) or affect bone mineral density (reviewed in Chui et al., 2024) but there are not yet any long-term studies using FGF21 mimetics. Long-term studies are needed to determine if and how FGF21 analogs impact bone health.

Drug interactions:

Not known. However, given the mechanism of action, FGF21 may interact with diabetes drugs (such as metformin or pioglitazone) and fibrates.

Research underway:

There are approximately eleven ongoing trials that are exploring the effects of FGF21 or FGF21 analogs in human patients. Most of these trials are for treatment of metabolic dysfunction-associated steatohepatitis (MASH) or related metabolic disorders.

There are three ongoing trials of pegozafermin / BIO89-100, a pegylated FGF21 analog. NCT06318169 (ENLIGHTEN-Fibrosis) is a 1-year blinded phase 3 RCT of pegozafermin in 1050 patients with stage 2 or 3 liver fibrosis in patients with metabolic dysfunction-associated steatohepatitis (MASH). NCT05852431 is a multi-year blinded phase 3 RCT in 762 patients with compensated cirrhosis due to MASH.

NCT06419374 is a blinded phase 3 RCT to assess the effect of pegozafermin on fasting triglyceride levels in 360 patients with severe hypertriglyceridemia.

There are four ongoing studies of efruxifermin, a bivalent Fc-FGF21 analog. NCT06215716 is a blinded phase 3 RCT of efruxifermin in 1000 patients with MASH and fibrosis. NCT06161571 is a blinded phase 3 RCT of efruxifermin in 700 patients with MASH / MASLD. NCT05039450 (Symmetry) is a blinded phase 2b RCT of efruxifermin in 200 patients with compensated cirrhosis due to MASH. NCT04767529 (Harmony) is a blinded phase 2b RCT of efruxifermin in 129 patients with MASH; interim results were published by Harrison et al., 2023.

NCT05655221 is a randomized controlled single ascending dose study assessing safety, tolerability, and immunogenicity of B1344 in 56 healthy adults. B1344 is an FGF21 analog that is being developed for nonalcoholic steatohepatitis (NASH). NCT04880031 is a blinded phase 2a RCT of BOS-580 in a total of 205 patients with obesity and at risk for, or with, MASH. NCT06143423 is a randomized controlled single and multiple ascending dose study investigating the safety and tolerability of AP026 (TQA2226), which is a FGF21-GLP-1 bifunctional fusion protein. The third trial is exploring the effects of FGF21 administration on taste and intake preferences, as well as glucose metabolism in healthy adult men (NCT04232033).

Search terms:

Pubmed, Google: FGF21

- Alzheimer's, longevity, aging, MASH/NASH, MASLD/NAFLD, bone, hypertriglyceridemia

Websites visited for FGF21

- Clinicaltrials.gov: FGF21; pegozafermin; efruxifermin; BOS-580
- PubChem: pegozafermin; efruxifermin
- DrugBank.ca: pegozafermin; efruxifermin
- Cafepharma

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