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.

Zilebesiran

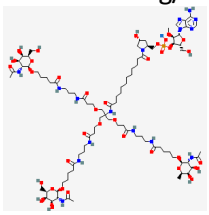
Evidence Summary

Zilebesiran is the first in class long-acting siRNA for hypertension targeting angiotensinogen undergoing clinical testing. It has shown reasonable safety and efficacy in combination with other antihypertensives.

Neuroprotective Benefit: Blood pressure lowering in the context of hypertension is associated with dementia risk reduction, but this association has not yet been specifically shown for zilebesiran.

Aging and related health concerns: Zilebesiran allows for stable long-acting blood pressure lowering. It is likely best suited for as part of a combinatorial approach in hypertensive patients resistant to monotherapy.

Safety: Injection site reactions are the most common adverse event in trials. It also has risks for hypotension and hyperkalemia, especially when used in combination with other antihypertensives. Lack of rapid reversibility is a potential safety risk.

Availability: In clinical trials	**Dose**: Not established. Administered via subcutaneous injection every six months. Tested doses include 150, 300, and 600 mg.	**Modified siRNA** **Chemical formula:** $C_{89}H_{152}N_{16}NaO_{36}P$ **MW**: 2076.2 g/mol  Source: PubChem
Half-life: A single dose reduces blood pressure for six months.	**BBB**: Not penetrant, liver restricted	
Clinical trials: Zilebesiran has been tested in Phase 1 (n=107), and Phase 2 trials (KARDIA-1 and 2) (n=377; n=672) in primary hypertension, with an additional Phase 2 trial (KARDIA-3) ongoing.	**Observational studies**: None	

What is it?

Zilebesiran is a small interfering RNA (siRNA) therapeutic targeting angiotensinogen that is currently in clinical development for hypertension by Alnylam Pharmaceuticals [1]. It targets the renin-angiotensin system (RAS) at a point further upstream than approved classes of oral antihypertensive agents. Due to the long-acting capacity of the siRNA, it effectively lowers angiotensinogen levels for at least six months, and has shown a durable effect on blood pressure lowering at tested doses with a twice a year administration schedule. It is currently in Phase 2 testing, and future studies will be needed to determine which approved antihypertensives combine with zilebesiran with the greatest safety and efficacy, as well as identify populations that may be at highest risk for adverse events.

Neuroprotective Benefit: Blood pressure lowering in the context of hypertension is associated with dementia risk reduction, but this association has not yet been specifically shown for zilebesiran.

Types of evidence:

- 0 meta-analyses or systematic reviews
- 0 clinical trials
- 0 observational studies
- 0 laboratory studies

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

Hypertension is a risk factor for dementia. Large clinical studies, such as SPRINT-MIND have found that intensive blood pressure control protects against cerebrovascular damage and cognitive decline [2]. Zilebesiran is expected to have a similar protective effect to previously tested antihypertensives, though its impact on dementia risk reduction has not yet been clinically tested.

Human research to suggest benefits to patients with dementia:

Zilebesiran has not yet been tested in dementia patients.

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

While it has indirect effects on brain health via mitigation of hypertension-related cerebrovascular damage, zilebesiran is a liver-targeted drug, and thus does not have any direct neuroprotective effects in the brain.

APOE4 interactions: Not established.

Aging and related health concerns: Zilebesiran allows for stable long-acting blood pressure lowering. It is likely best suited for as part of a combinatorial approach in hypertensive patients resistant to monotherapy.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 3 clinical trials in primary hypertension (1 Phase 1 and 2 Phase 2)
- Several laboratory studies

Hypertension: POTENTIAL BENEFIT

Hypertension, or high blood pressure, is one of the major risk factors for cardiovascular disease. Several classes of antihypertensives have been developed which are used by millions of people globally. Despite

this, blood pressure remains inadequately controlled (>130/80 mmHg) in a large percentage of people with hypertension [3]. This is due to suboptimal efficacy of monotherapy for many patients, as well as a lack of medication adherence. Novel antihypertensives that work well in combination with existing therapies and require infrequent administration may allow a greater percentage of individuals to achieve recommended blood pressure targets.

The renin-angiotensin-system (RAS) is a hormonal system that regulates blood pressure, blood volume, and electrolyte balance by regulating extracellular fluid volume [1]. Renin is a hormone and enzyme secreted by the kidneys when renal blood flow is reduced which facilitates the conversion of liver derived angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and stimulates the secretion of aldosterone, which regulates electrolyte balance by promoting the reabsorption of sodium and excretion of potassium. These changes lead to an increase in blood pressure. Several classes of approved antihypertensives target this pathway, including ACE inhibitors and angiotensin II receptor blockers (ARBs). However, due to a negative feedback loop, intervening at these points can lead to a compensatory increase in renin.

Zilebesiran is designed to act upstream in the RAS cascade, by targeting liver-derived angiotensinogen. It is a small-interfering RNA (siRNA) that is targeted to the liver through the use of the trivalent N-acetylgalactosamine (GalNAc) modification, which binds to the asialoglycoprotein receptor, which is abundantly expressed on hepatocytes [1]. The targeted siRNA is taken up by hepatocytes and accumulates in intracellular acidic compartments, where it is remarkably stable, allowing for release of functional siRNA weeks after administration. This is the same liver targeting system used for other approved and clinically tested siRNAs, such as the PCSK9 targeting siRNA, inclisiran. To date, this siRNA system has shown superiority in targeting angiotensinogen for blood pressure control relative to an antisense oligonucleotide (ASO) approach. Development of the IONIS-AGT-L_{Rx} ASO was discontinued following its inability to significantly lower blood pressure in Phase 2 trials, despite robust lowering of angiotensinogen [4].

Zilebesiran is currently in Phase 2 clinical testing for primary hypertension. Full study results have been published for a Phase 1 trial and the Phase 2 KARDIA-1 trial, while results for the Phase 2 KARDIA-2 trial have been presented at the 2024 American College of Cardiology (ACC) Annual Scientific Session, but not yet published in a peer-reviewed journal.

A meta-analysis of these three RCTs (n=1,145) found that zilebesiran was associated with a significant reduction in 24-hour systolic blood pressure across all doses relative to placebo (Mean Difference [MD]:

-12.84, 95% Confidence Interval [CI] -16.00 to -9.68; P < 0.00001). A significant lowering of office systolic blood pressure was also achieved with zilebesiran treatment (MD: -11.10, 95% CI -13.66 to -8.55; P < 0.00001) [5]. As a confirmation of target engagement, plasma levels of angiotensinogen were significantly reduced with zilebesiran (MD: -0.99, 95% CI -1.06 to -0.93; P < 0.00001).

The Phase 1 trial (NCT03934307) tested single subcutaneous doses of zilebesiran (10, 25, 50, 100, 200, 400, or 800 mg) [6]. Decreases in systolic blood pressure of >10 mmHg were observed by week eight after doses of 200 mg and above, with a reduction of -22.5±5.1 mmHg observed at week 24 in the eight participants treated at the 800 mg dose. The reduction in blood pressure with zilebesiran was shown to be sensitive to the level of salt in the diet, such that participants on a low-salt diet had a reduction in systolic blood pressure of -18.8±4.3 mmHg following 800 mg of zilebesiran, but blood pressure returned to baseline while on a high-salt diet. The addition of the ARB class antihypertensive irbesartan had only a marginal additional impact on blood pressure lowering in combination with 800 mg zilebesiran.

The randomized, double-blind, placebo-controlled Phase 2 KARDIA-1 trial (NCT04936035) achieved its primary endpoint of between-group difference in least-squares mean (LSM) change from baseline to month three in 24-hour mean ambulatory systolic blood pressure (see table) [7]. Participants were randomized to placebo every three months, or subcutaneous doses of 150 mg, 300 mg, or 600 mg zilebesiran once every six months, or a subcutaneous dose of 300 mg zilebesiran every three months. The full analysis set included 377 participants, 347 of which completed the entire six-month study period. Zilebesiran also achieved secondary endpoints, including significant reductions in office systolic blood pressure at three months and six months, as well as reductions in diastolic blood pressure and serum angiotensinogen levels. A lower percentage of participants treated with zilebesiran required rescue medication over the treatment period compared to those treated with placebo (20.5% to 32.1% vs. 52.0%).

	150 mg every 6 months (n=78)	300 mg every 3 or 6 months (n=148)	600 mg every 6 months (n=76)	Placebo (n=75)
LSM change (95% CI) in 24-hr ambulatory SBP at 3 months	-7.3 mmHg (-10.3 to -4.4)	-10.0 mmHg (-12.0 to -7.9)	-8.9 mmHg (-11.9 to -6.0)	+6.8 mmHg (3.6 to 9.9)
LSM change (95% CI) in 24-hr ambulatory DBP at 3 months	-4.5 mmHg (-6.1 to -2.9)	-5.7 mmHg (-6.8 to -4.5)	-5.8 mmHg (-7.4 to -4.1)	3.5 mmHg (1.8 to 5.2)

LSM change (95%CI) in office SBP at 3 months	-9.7 mmHg (-12.6 to -6.8)	-12.1 mmHg (-14.2 to -10.0)	-9.2 mmHg (-12.1 to -6.2)	-0.1 mmHg (-3.2 to 3.0)

Due to the slow onset of maximum blood pressure reduction achieved with zilebesiran relative to conventional antihypertensives, its likely clinical utility will be for use in combination with other antihypertensives in those with inadequately controlled blood pressure with conventional therapies alone [3].

The ability of zilebesiran to have an additive effect in blood pressure lowering when combined with conventional classes of antihypertensives was assessed in the randomized, double-blind, placebo-controlled Phase 2 KARDIA-2 trial (NCT051033320). Participants were randomized to the thiazide-like diuretic (indapamide 2.5 mg), calcium channel blocker (amlodipine 5mg) or ARB (olmesartan 40 mg) and treated for four weeks. Participants for whom blood pressure remained inadequately controlled were then randomized to add a single subcutaneous dose of 600 mg zilebesiran or placebo and followed for six months. The primary analysis reported at 2024 ACC Annual Scientific Session included 672 patients. The primary endpoint of the change in ambulatory 24-hour mean systolic blood pressure was met for all zilebesiran treated groups, however, the additive effect was weakest with the use of an antihypertensive that acts on the same (RAS) pathway as zilebesiran, the ARB olmesartan, relative to those that act on different pathways (indapamide and amlodipine) (see table) (Press release).

	Indapamide (2.5 mg) (n=110)		Amlodipine (5 mg) (n=205)		Olmesartan (40 mg) (n=251)	
Placebo adjusted change from baseline to 24-Hr mean SBP	- 12.1 mmHg		- 9.7 mmHg		- 4.0 mmHg	
Placebo-adjusted change from baseline to month 3 in office SBP	- 18.5 mmHg		- 10.2 mmHg		- 7.0 mmHg	
proportion of patients with 24-Hr mean SBP <130 mmHg and/or reduction ≥20 mmHg without rescue antihypertensive medication at month 6	Placebo (n=57) 14%	Zilebesiran (n=53) 64.2%	Placebo (n=102) 13.7%	Zilebesiran (n=103) 39.8%	Placebo (n=134) 17.2%	Zilebesiran (n=117) 26.5%

The ongoing KARDIA-3 study (NCT06272487) assesses the efficacy and safety of zilebesiran as add-on therapy in patients who have established cardiovascular disease or high cardiovascular risk with or without advanced chronic kidney disease.

A key outstanding question to be addressed in large future studies is whether zilebesiran effectively lowers the risk for adverse cardiovascular events and cardiovascular-related mortality [8].

Safety: Injection site reactions are the most common adverse event in trials. It also has risks for hypotension and hyperkalemia, especially when used in combination with other antihypertensives. Lack of rapid reversibility is a potential safety risk.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 3 clinical trials in primary hypertension (1 Phase 1 and 2 Phase 2)
- Several laboratory studies

Zilebesiran has been generally well-tolerated in clinical trials to date in patients with primary hypertension, with injection site reactions as the most common adverse events [9].
In the 24-week Phase 1 trial (n=107), testing single doses of zilebesiran from 10 mg to 800 mg, the most common adverse events were headache, injection site reactions, and upper respiratory tract infections, though rates were generally similar between the zilebesiran and placebo-treated groups [6]. There were no cases of hypotension, hyperkalemia (elevated potassium), or kidney impairment, nor clinically significant changes in body weight, or serum levels of potassium, sodium, or creatinine, or in the estimated glomerular filtration rate (eGFR). Transient, low-titer anti-drug antibodies were detected in 2% of patients.

In the 24-week Phase 2 KARDIA-1 trial (n=377), drug-related adverse events were mild to moderate in severity, with injection site reactions (6.3% vs 1.3%) and mild hyperkalemia (5.3% vs 0%) more common with zilebesiran compared to placebo [7]. Injection site reactions were more common with dosing every three months, relative to every six months. Seventeen zilebesiran-treated participants experienced serum potassium levels >5.5 mmol/L, while two of these participants experienced levels >6 mmol/L. Three participants were treated for hyperkalemia, but did not lead to drug discontinuation. Clinically relevant treatment-emergent adverse events occurring more frequently with zilebesiran included acute

kidney injury (1.3% vs 0%), hepatic adverse events (3.0% vs 1.3%), hypotension (4.3% vs 1.3%), and hyperkalemia (6.3% 2.7%). With respect to the hepatic events, 2.3% of zilebesiran-treated participants experienced elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of at least 3-fold the upper limit of normal (ULN), and none experienced total bilirubin elevations of at least 2-fold the ULN. Changes from baseline in serum creatinine, eGFR, and glucose levels were similar between those treated with zilebesiran and placebo.

Full safety results are not yet available for the 24-week Phase 2 KARDIA-2 trial, but presented results indicate that no new safety concerns emerged when combining zilebesiran with approved classes of anti-hypertensives, including diuretics, calcium channel blockers, and ARBs (Press release). Overall rates of adverse events were similar across treatment groups. Rates of hypotension/orthostatic hypotension were more frequent with zilebesiran in those taking the calcium channel blocker amlodipine (5.9% vs 3.3%) or the ARB olmesartan (4.7% vs 2%). Rates of hyperkalemia (>5.5mmol/L) (3.2% to 6.8% vs 0% to 2%), and evidence of kidney impairment based on ≥30% decrease in eGFR (6.7% to 12.7% vs 1.6% to 4.1%) were more common with zilebesiran compared with placebo, but these tended to occur within the first three months of treatment and resolved on their own.

A key concern regarding the use of a long-acting RAS antagonist is potential for acute recovery of RAS function during instances of hypotension and trauma, such as a bleeding event or cardiac injury. Evidence from the Phase 1 trial and preclinical studies indicates that the effects of zilebesiran are reversible in the context of a high-salt diet, thus i.v. NaCl (salt) administration may offer clinical utility in those situations [10]. Alnylam Pharmaceuticals is also developing a system to antagonize the angiotensinogen siRNA, called REVERSIR™, to be used as a potential reversible mechanism [1]. REVERSIR™ is an oligonucleotide that is complementary to the therapeutic siRNA (i.e. zilebesiran) to reverse gene silencing.
Another physiological event which requires a functional RAS is pregnancy. Blockade of this system during pregnancy can impair necessary physiological adaptations and can harm the fetus. Due to the long-acting nature of zilebesiran, it is likely that its use will not be recommended in women of childbearing age [10].

Due to the RAS negative feedback loop, declining levels of angiotensin II induce an increase in the secretion of renin, leading to a rise in plasma renin levels [1]. One study suggests that zilebesiran may increase renin levels to a greater degree than existing classes of anti-hypertensives acting on the RAS,

such as ARBs (i.e. irbesartan) (Company presentation). The potential consequences of chronically high renin levels, and the risk for kidney damage remain unclear.
Drug interactions: Interactions have not yet been established, but combining zilebesiran with other drugs targeting the RAS, such as ACE inhibitors or ARBs may increase the risk for side effects, such as hyperkalemia and kidney injury. Additionally, the Phase 2 KARDIA-2 study suggests that the additive benefit of ARBs is lower relative to its use in combination with other classes of antihypertensives (i.e. diuretics and calcium channel blockers).

Sources and dosing:

Zilebesiran is still in clinical development and is not yet approved for any indication. It is in clinical development by Alnylam® Pharmaceuticals. It is administered via subcutaneous injection once every six months. It has been shown to significantly reduce blood pressure at doses ranging from 150 mg to 600 mg, however, higher doses do not necessarily confer greater efficacy [3]. A meta-analysis suggests that the optimal dosing range is likely between 250 mg and 500 mg [5].

Research underway:

According to Clinicaltrials.gov, there are currently two active clinical trials testing zilebesiran.

A Phase 1/2, randomized, double-blind, placebo-controlled, parallel-group study is evaluating the safety, tolerability, efficacy, pharmacodynamics, and pharmacokinetics of zilebesiran in Japanese patients with mild to moderate hypertension (NCT06423352). The trial has an expected completion date in late 2025.

The randomized, double-blind, placebo-controlled, Phase 2 KARDIA-3 trial is evaluating the efficacy and safety of zilebesiran used as add-on therapy in adult patients with high cardiovascular risk and hypertension not adequately controlled by standard of care antihypertensive medications conditions (n=375) (NCT06272487). Participants must be on stable doses of at least 2, but not more than 4, antihypertensive medications for at least 30 days prior to screening and remain on stable doses of those medications for the study duration. The primary outcome is the change from baseline in mean seated office systolic blood pressure at month 3. The trial has an expected completion date in 2025.

Search terms:

Pubmed, Google: Zilebesiran

- Hypertension, Cardiovascular disease, Clinical trials, Meta-analysis, Safety

Websites visited for Zilebesiran:

- Clinicaltrials.gov
- PubChem
- DrugBank.ca
- Cafepharma

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