Zilebesiran: Mechanism of Action

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The safety and efficacy of zilebesiran are currently being investigated in clinical studies and have not been evaluated by the FDA or any health authority.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic that reduces the synthesis of hepatic AGT. By targeting the most upstream precursor of the RAAS, zilebesiran is designed to reduce serum AGT levels, leading to a reduction in blood pressure.[1]

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RNA INTERFERENCE

RNAi is a natural endogenous intracellular catalytic mechanism that regulates gene expression. RNAi utilizes siRNAs that are loaded onto a ribonucleoprotein complex known as the RISC to cleave and degrade specific mRNA, resulting in reduced production of the target protein.[2–4]

RNAi therapeutics utilize synthetic siRNA. GalNAc-conjugated siRNAs are designed to target and degrade specific mRNA in the liver following subcutaneous administration, thereby reducing the production of certain proteins.[5]

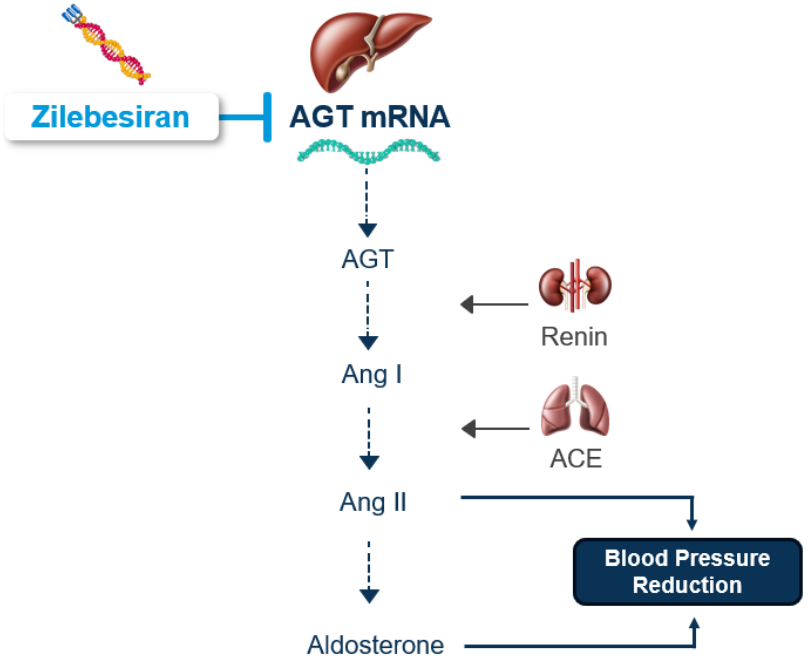
MECHANISM OF ACTION

Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic that reduces the synthesis of hepatic AGT. AGT is primarily produced in the liver and is the sole precursor of all angiotensin peptides, including Ang II and aldosterone. By targeting the most upstream precursor of the RAAS, zilebesiran is designed to reduce serum AGT levels, leading to a reduction in blood pressure (**Figure 1**). RAAS inhibition with this approach may theoretically limit compensatory angiotensin activation associated with angiotensin-converting-enzyme inhibition or angiotensin-receptor blockade.[1]

Zilebesiran consists of a synthetic siRNA covalently linked to a GalNAc ligand that binds with high affinity to the hepatic ASGPR, enabling targeted delivery to the liver.[1] Following hepatocyte uptake, the siRNA associates with the RISC to enable complementary pairing with *AGT* mRNA, resulting in target

mRNA cleavage and degradation. A single zilebesiran siRNA remains bound to the RISC for multiple cleavage cycles, acting in a catalytic manner.[6–8]

Figure 1. Zilebesiran Mechanism of Action.[1,9]



Abbreviations: ACE = angiotensin-converting enzyme; AGT = angiotensinogen; Ang I = angiotensin I; Ang II = angiotensin II; mRNA = messenger ribonucleic acid.

ABBREVIATIONS

ACE = angiotensin-converting enzyme; AGT = angiotensinogen; Ang I = angiotensin I; Ang II = angiotensin II; ASGPR = asialoglyoprotein receptor; GalNAc = N-acetylgalactosamine; mRNA = messenger ribnonucleic acid; RAAS = renin-angiotensin-aldosterone system; RISC = RNA-induced silencing complex; RNAi = ribonucleic acid interference; siRNA = small interfering ribonucleic acid.

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