

Zilebesiran Therapeutic Hypothesis

Target:

Angiotensinogen (AGT)¹

siRNA delivery technology:

GalNAc conjugation¹

Dysregulation of the RAAS plays a critical role in hypertension and may also independently contribute to end organ damage, primarily through the potent vasoconstrictor Ang II¹⁻⁶

AGT mRNA
in the liver

Zilebesiran

ANGIOTENSINOGEN
(AGT)

decreased

Renin

ANGIOTENSIN I

decreased

ACE

ANGIOTENSIN II

decreased

Reduced
activation of the
receptor

BLOOD
PRESSURE

reduced

Ang II type 1
receptor

AGT is the most upstream and sole precursor of all angiotensin peptides^{1,3,4,7}

Zilebesiran targets AGT mRNA in the liver, reducing the production of AGT^{1,7,8}

Figure adapted from Cruz-López et al. 2022³ and Touyz 2023.⁸ ACE, angiotensin-converting enzyme; AGT, angiotensinogen; Ang, angiotensin; GalNAc, N-acetylgalactosamine; mRNA, messenger RNA; RAAS, renin-angiotensin-aldosterone system; RNA, ribonucleic acid; siRNA, small interfering RNA. 1. Desai AS et al. *N Engl J Med*. 2023;389(3):228–38. 2. Benigni A et al. *EMBO Mol Med*. 2010;2(7):247–57. 3. Cruz-López EO et al. *Hypertension*. 2022;79(10):2115–26. 4. Morgan ES et al. *JACC Basic Transl Sci*. 2021;6(6):485–96. 5. Iwanami J et al. *Hypertens Res*. 2009;32(4):229–37. 6. Ibrahim MM. *J Hum Hypertens*. 2006;20(2):101–8. 7. Bakris GL et al. *JAMA*. 2024;331(9):740–9. 8. Touyz RM. *N Engl J Med*. 2023;389(3):278–81.