Impact of Zilebesiran, an Investigational RNA Interference Therapeutic Targeting Hepatic Angiotensinogen, on Renin–Angiotensin System Biomarkers in Patients with Mild-to-Moderate Hypertension

Michael Weber[1], Manish Saxena[2,3], Michel Azizi[4,5], Rajvir S Chauhan[6], Jongtae Lee[6], Nitender Goyal[6], Dion Zappe[6], Akshay S Desai[7]

[1]SUNY Downstate College of Medicine, SUNY Downstate Health Sciences University, New York, NY, USA; [2]Barts Health NHS Trust, London, UK; [3]Queen Mary University of London, London, UK; [4]Université Paris Cité, Paris, France; [5]Hôpital Européen Georges-Pompidou, Paris, France; [6]Alnylam Pharmaceuticals, Cambridge, MA, USA; [7]Brigham & Women's Hospital, Boston, MA, USA

Conclusions

- **Zilebesiran is an RNA interference (RNAi) therapeutic that targets hepatic synthesis of angiotensinogen (AGT), the most upstream precursor of the renin–angiotensin–aldosterone system (RAAS).**
- **In the KARDIA-1 study, biannual or quarterly doses of zilebesiran demonstrated rapid and robust reductions in serum AGT, angiotensin I and II, and aldosterone, as well as increases in plasma renin concentrations sustained to Month 6, compared with minimal changes with placebo.**
- **Despite increases in plasma renin concentration, consistent suppression of aldosterone was observed through Month 6, with no evidence of angiotensin escape or aldosterone breakthrough during this period.**
- **Together, these findings demonstrate the differentiated mechanism of action of zilebesiran in suppressing all downstream substrates of AGT and support a biannual dosing regimen for zilebesiran.**

Introduction

Background

- AGT is the most upstream precursor of the RAAS and is the only known substrate of renin, playing a central role in controlling downstream RAAS effects and regulating blood pressure (BP) control.[1–3]
- Existing oral antihypertensives (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) that target RAAS downstream of AGT can result in compensatory rises in renin by the kidney, leading to loss of angiotensin II inhibition and attenuation of treatment response over time.[1,4]
- Enzymatic cleavage of AGT by renin is a rate-limiting step of the RAAS; thus, targeting this initial step is a pharmacologically rational strategy to suppress RAAS activity.

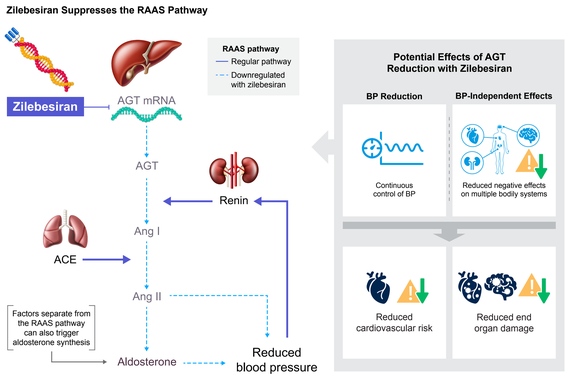
Zilebesiran

- Zilebesiran is an investigational RNAi therapeutic that reduces hepatic synthesis of AGT for up to 6 months following a single subcutaneous (SC) injection.[5]
- Targeting AGT leads to downstream suppression of the RAAS[2,5–7] and offers continuous suppression of the RAAS, with the potential to produce BP-dependent and BP-independent effects (**Figure 1**).
- In KARDIA-1, a Phase 2 study of zilebesiran treatment for patients with hypertension, biannual or quarterly dosing resulted in sustained BP control over 6 months compared with placebo.[5]
  - For 24-hour mean ambulatory systolic BP (SBP), significant placebo-adjusted least-squares mean reductions from baseline were up to 16.7 mmHg and 14.5 mmHg at Months 3 and 6 (all comparisons $p<0.001$; primary endpoint).

Objective

- This analysis aims to investigate the effects of zilebesiran on RAAS in patients with mild-to-moderate hypertension in the KARDIA-1 study (NCT04936035).

Figure 1. Zilebesiran Therapeutic Hypothesis



ACE, angiotensin-converting enzyme; AGT, angiotensinogen; Ang, angiotensin; BP, blood pressure; mRNA, messenger RNA; RAAS, renin–angiotensin–aldosterone system.

Methods

- KARDIA-1 was a Phase 2, double-blind, placebo-controlled study assessing efficacy, safety, and pharmacodynamics of zilebesiran in patients with mild-to-moderate hypertension.
- Eligible patients discontinued prior antihypertensive therapy for at least 2 weeks, and those with mean daytime ambulatory SBP 135–160 mmHg were randomized equally to receive zilebesiran SC (150, 300, or 600 mg once every 6 months [Q6M] or 300 mg once every 3 months [Q3M]) or placebo SC Q3M. Patients were advised to limit sodium consumption to approximately 2.0 g per day.
- Here, we report the change from baseline to Months 3 and 6 in serum AGT, plasma renin concentration, and serum angiotensin I and II and aldosterone concentrations (exploratory endpoints).

Results

Patient Population

- In total, 377 patients were analyzed (zilebesiran, N=302; placebo, N=75). Baseline demographics were consistent across cohorts.[6]
  - The mean (standard deviation) age of patients was 56.8 (10.6) years, 55.7% of patients were male, and 24.7% were Black or African American.
- Baseline levels of RAAS were mostly similar across groups; aldosterone varied between cohorts (**Table 1**).

Table 1. Median RAAS Levels at Baseline

	Zilebesiran				Placebo (N=75)
	150 mg Q6M (N=78)	300 mg Q6M (N=73)	300 mg Q3M (N=75)	600 mg Q6M (N=76)	
Plasma renin concentration, mIU/L[a]	11.7 (5.4, 19.4)	12.2 (4.8, 25.8)	10.8 (4.9, 19.6)	10.3 (4.6, 16.3)	10.6 (4.2, 21.8)
Serum angiotensin I, pmol/L	18.9 (11.0, 33.0)	20.6 (10.5, 35.1)	14.8 (8.9, 29.3)	16.4 (10.6, 35.7)	16.1 (8.4, 35.8)
Serum angiotensin II, pmol/L	53.0 (32.4, 92.0)	57.0 (28.3, 115.5)	46.9 (25.0, 70.5)	48.3 (26.2, 96.8)	48.9 (21.4, 106.6)
Serum aldosterone, pmol/L	187.1 (125.3, 287.2)	200.8 (126.5, 300.9)	141.6 (84.9, 217.3)	158.5 (88.5, 250.3)	172.3 (105.2, 252.7)

Plasma and serum blood samples for RAAS assessment were collected in the morning with the patient in a seated or upright position. Serum AGT levels were measured using validated ELISA. Plasma renin concentration was measured using a chemiluminescence immunoassay. Serum angiotensin I and II and aldosterone were measured by liquid chromatography tandem mass spectrometry-based RAAS equilibrium fingerprint analysis.

Data are shown as median (Q1, Q3). Baseline was considered the last assessment before receiving the first dose of study drug.

[a]n=76, 71, 75, 72, and 72 for the 150 mg Q6M, 300 mg Q6M, 300 mg Q3M, 600 mg Q6M, and placebo groups, respectively.

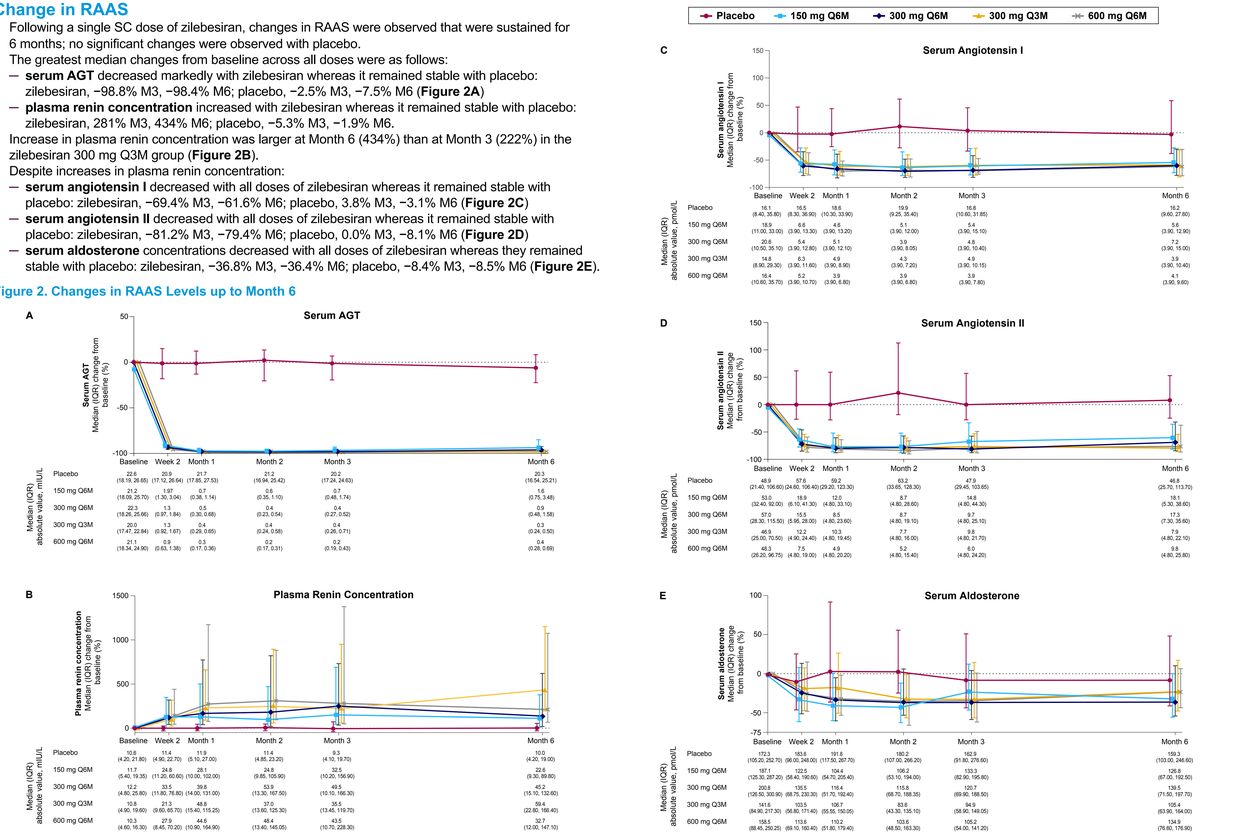
AGT, angiotensinogen; ELISA, enzyme-linked immunosorbent assay; Q1, first quartile; Q3, third quartile; Q3M, every 3 months; Q6M, every 6 months; RAAS, renin–angiotensin–aldosterone system.

Results cont.

Change in RAAS

- Following a single SC dose of zilebesiran, changes in RAAS were observed that were sustained for 6 months; no significant changes were observed with placebo.
- The greatest median changes from baseline across all doses were as follows:
  - **serum AGT** decreased markedly with zilebesiran whereas it remained stable with placebo: zilebesiran, −98.8% M3, −98.4% M6; placebo, −2.5% M3, −7.5% M6 (**Figure 2A**)
  - **plasma renin concentration** increased with zilebesiran whereas it remained stable with placebo: zilebesiran, 281% M3, 434% M6; placebo, −5.3% M3, −1.9% M6.
- Increase in plasma renin concentration was larger at Month 6 (434%) than at Month 3 (222%) in the zilebesiran 300 mg Q3M group (**Figure 2B**).
- Despite increases in plasma renin concentration:
  - **serum angiotensin I** decreased with all doses of zilebesiran whereas it remained stable with placebo: zilebesiran, −69.4% M3, −61.6% M6; placebo, 3.8% M3, −3.1% M6 (**Figure 2C**)
  - **serum angiotensin II** decreased with all doses of zilebesiran whereas it remained stable with placebo: zilebesiran, −81.2% M3, −79.4% M6; placebo, 0.0% M3, −8.1% M6 (**Figure 2D**)
  - **serum aldosterone** concentrations decreased with all doses of zilebesiran whereas they remained stable with placebo: zilebesiran, −36.8% M3, −36.4% M6; placebo, −8.4% M3, −8.5% M6 (**Figure 2E**).

Figure 2. Changes in RAAS Levels up to Month 6



AGT, angiotensinogen; IQR, interquartile range; Q3M, every 3 months; Q6M, every 6 months; RAAS, renin–angiotensin–aldosterone system.

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