Home Blood Pressure Reductions with Zilebesiran in Patients with Mild-to-Moderate Hypertension are Consistent with Ambulatory and Office Blood Pressure Reductions in the KARDIA-1 Study

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Conclusions

- **In KARDIA-1, treatment with zilebesiran compared with placebo resulted in clinically significant time-adjusted reductions in self-assessed home systolic blood pressure (SBP) at 3 and 6 months, which were largely consistent with time-adjusted ambulatory and office SBP reductions.**
- **Time in target range assessed by home SBP monitoring was greater in patients treated with zilebesiran than placebo.**
  - **The results presented here suggest the potential utility of home blood pressure (BP) monitoring in assessing time in target range, which has the benefit of enabling more frequent BP assessments over a given period of time.**
- **Regardless of the mode in which BP was assessed, consistent SBP reductions through 6 months were observed following treatment with a subcutaneous dose of zilebesiran versus placebo. Moreover, this indicates that self-monitoring of BP at home during biannual zilebesiran therapy demonstrated additional evidence of continuous control outside the clinical visit setting.**

Background

- BP can fluctuate over time, and BP variability (BPV) is associated with a greater risk of cardiovascular events independent of average BP.[1,2]
- BPV is influenced, in part, by inadequate BP control with conventional oral antihypertensive medications and by poor adherence to treatment regimens.[3,4]
  - A combination of office and out-of-office BP measurements is often used in the management of hypertension, and home BP monitoring can be used to obtain a large number of measurements in a familiar setting for patients.[5]
- In the KARDIA-1 study, a single subcutaneous dose of zilebesiran, an investigational RNA interference therapeutic that targets hepatic angiotensinogen, demonstrated significant reductions in ambulatory and office SBP compared with placebo at 3 months, which were sustained for up to 6 months.[6]
- Here we present KARDIA-1 results on time-adjusted home, ambulatory, and office SBP at 3 and 6 months, as well as time in target range assessed by home SBP monitoring to characterize the impact of zilebesiran on providing continuous control of blood pressure.

Methods

KARDIA: Dose-Ranging Phase 2 Study Assessing the Efficacy and Safety of Zilebesiran Monotherapy in Adult Patients with Mild-to-Moderate Hypertension

- Untreated hypertension or stable therapy with ≤2 antihypertensive medications
- Washout of previous antihypertensives for ≥2 weeks
- Daytime mean ambulatory SBP 135–160 mmHg

Placebo Q3M SC
Zilebesiran 150 mg Q6M SC
Zilebesiran 300 mg Q6M SC
Zilebesiran 300 mg Q3M SC
Zilebesiran 600 mg Q6M SC

Rescue permitted[a]

Baseline M3 M6

Change from baseline at M3 and M6 in SBP was assessed by:

Ambulatory BP monitoring (SunTech Oscar 2M250)
BP measurements taken at regularly scheduled visits with an automated device

24-hr mean ambulatory BP monitoring
Average of hourly means of readings taken every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am)

Daytime mean ambulatory BP monitoring
Average of hourly means of readings taken every 20 minutes during the day (6 am to 9:59 pm)

Office BP monitoring (Microlife WatchBP Office 2G)
Seated BP measurements taken at regularly scheduled visits with an automated device[b]

Home BP monitoring (Microlife WatchBP Office 2G)
Weekly average of readings taken by the patient approximately once a week using an automated device, measured seated in the morning upon waking, before breakfast/caffeine, or before taking morning oral medications[b,c]

BP data were summarized as:

Time-adjusted BP (all modes of BP assessment)
Area under the curve (a measure of cumulative BP) divided by time interval, providing a weighted average of change from baseline to each scheduled visit

Time at target (home BP monitoring)
Percentage time in the target range (mean seated average weekly home SBP <130 mmHg)

ClinicalTrials.gov: NCT04936035
Full methods are described in Bakris *et al.* 2024.[6]
[a]Rescue antihypertensive medication was permitted between M3 and M5. [b]Measurements were taken after a 5-minute rest period. The mean of three readings was used. [c]Exploratory endpoint.
BP, blood pressure; hr, hour; M, Month; Q3M, every 3 months; Q6M, every 6 months; SC, subcutaneous.

Results

Patient Population and Baseline Characteristics

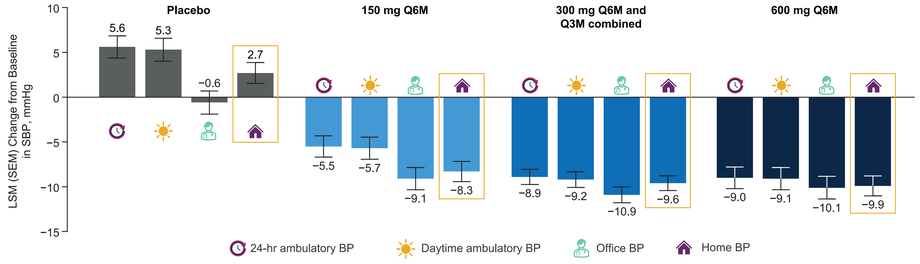
- **377** patients received treatment
- **44.3%** female
- **56.8** years (mean age)
- **27.3%** aged ≥65 years
- **24.7%** Black/African American
- **56.8%** BMI ≥30 kg/m²
- **72.4%** received antihypertensive medication before the study
- **141.8 mmHg** mean 24-hr mean ambulatory SBP
- **141.8 mmHg** mean office SBP

BMI, body mass index; hr, hour; SBP, systolic blood pressure.

Efficacy

- Clinically significant time-adjusted reductions in self-assessed home SBP with zilebesiran versus placebo were largely consistent with time-adjusted reductions in ambulatory and office SBP at Month 3 (**Figure 1**).

Figure 1. Time-Adjusted SBP Through Month 3



BP assessments were censored if taken while patients were receiving, or in the 2 weeks after stopping, any rescue medication. Time-adjusted change from baseline is the area under the curve divided by the time interval. For analyses of Month 3 endpoints, zilebesiran 300 mg Q3M and Q6M data were pooled together because patients in both cohorts had received the same amount of study drug at this point. Time-adjusted SBP at Month 3 was estimated between Week 4 and Week 12. LSMs were derived from mixed model for repeated measures including treatment, visit, treatment-by-visit interaction, and race as fixed factors and corresponding baseline SBP as a covariate. LSM difference in placebo vs zilebesiran for all zilebesiran doses and all BP measurement types: $p<0.0001$.
BP, blood pressure; hr, hour; LSM, least-squares mean; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; SEM, standard error of the mean.

- Treatment with each dose of zilebesiran resulted in an increased time in target range evaluated by home BP monitoring compared with placebo (**Table 1**).

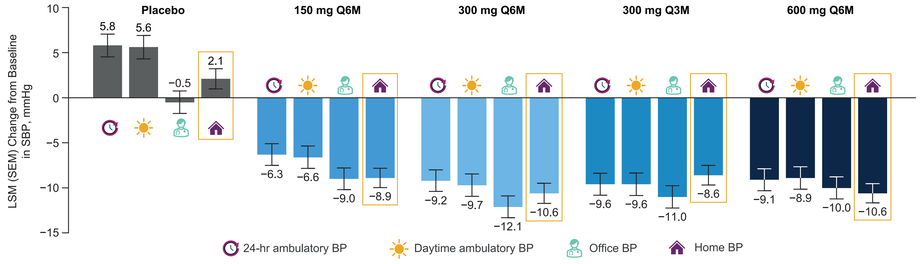
Table 1. Percentage Time in Target Range (SBP <130 mmHg) by Home SBP Between Months 1 and 6

Percentage time in target range	Placebo (N=75)	Zilebesiran 150 mg Q6M (N=78)	Zilebesiran 300 mg Q6M (N=73)	Zilebesiran 300 mg Q3M (N=75)	Zilebesiran 600 mg Q6M (N=76)
n	65	72	69	71	70
Mean % (SD)	21.9 (30.3)	54.2 (39.5)	55.1 (37.1)	61.7 (36.6)	61.3 (37.5)
Median %	5.9	61.7	63.4	66.0	72.4

Blood pressure assessments were censored if taken while patients were receiving, or in the 2 weeks after stopping, any rescue medication.
Percentage time in target range is estimated between Week 4 and Week 24 up to the last observed assessment using linear interpolation.
n, number of patients with available data; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; SD, standard deviation.

- Clinically significant time-adjusted reductions in home SBP with zilebesiran versus placebo were sustained through Month 6, consistent with time-adjusted reductions in ambulatory and office SBP (**Figure 2**).

Figure 2. Time-Adjusted SBP Through Month 6



BP assessments were censored if taken while patients were receiving, or in the 2 weeks after stopping, any rescue medication. Time-adjusted change from baseline is the area under the curve divided by the time interval. Time-adjusted SBP at Month 6 was estimated between Week 4 and Week 24. LSMs were derived from mixed model for repeated measures including treatment, visit, treatment-by-visit interaction, and race as fixed factors and corresponding baseline SBP as a covariate. LSM difference in placebo vs zilebesiran for all zilebesiran doses and all BP measurement types: $p<0.0001$.
BP, blood pressure; hr, hour; LSM, least-squares mean; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; SEM, standard error of the mean.

REFERENCES

1. Rothwell PM *et al. Lancet* 2010;375:895–905.
2. Oishi E *et al. Circulation* 2017;136:516–25.
3. De la Sierra A. *J Clin Med* 2023;12:6167.
4. Parati G *et al. J Hypertens* 2023;41:527–44.
5. Bouboucha Papoulou N *et al. Hypertens Res* 2021;44:1617–24.
6. Bakris GL *et al. JAMA* 2024;331:740–9.

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