Safety and Tolerability of Zilebesiran, an RNA Interference Therapeutic Targeting Hepatic Angiotensinogen Synthesis, in Obese Patients with Hypertension

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Presenter Disclosures

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SAFETY AND TOLERABILITY OF ZILEBESIRAN, AN RNA INTERFERENCE THERAPEUTIC TARGETING HEPATIC ANGIOTENSINOGEN SYNTHESIS, IN OBESE PATIENTS WITH HYPERTENSION

FINANCIAL DISCLOSURE:

Jorg Taubel has served as principal investigator in complete and ongoing clinical trials funded by Alnylam Pharmaceuticals.

UNLABELED/UNAPPROVED USES DISCLOSURE:

Zilebesiran is an investigational product in development for treatment of patients with hypertension.

Background

Hypertension

- Uncontrolled hypertension is a leading cause of morbidity and mortality[1–3]
- Many patients with hypertension are overweight or obese,[4,5] which can potentially influence the safety and efficacy of subcutaneously administered drugs[6]

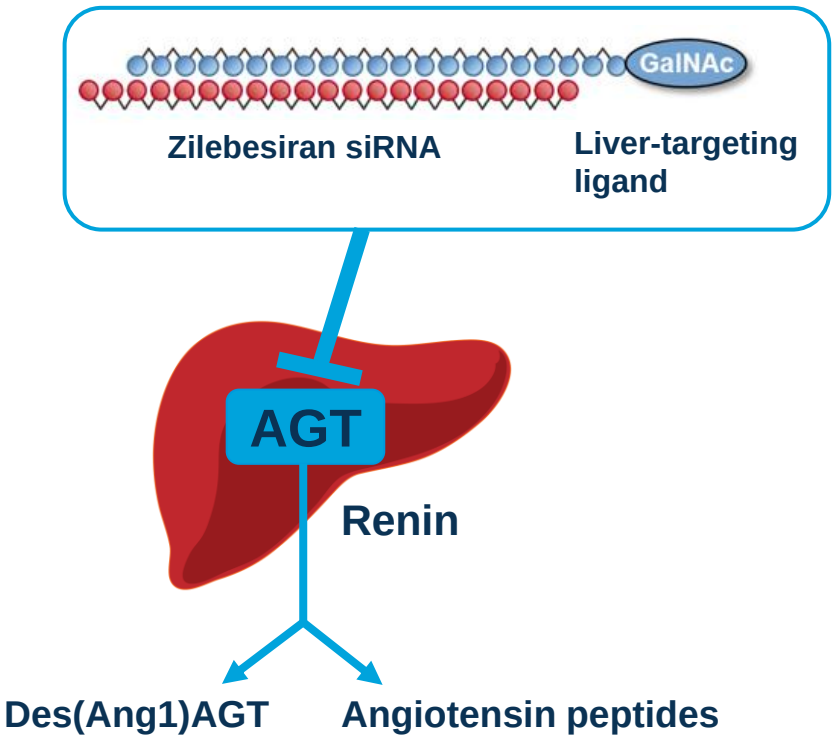
Zilebesiran

- Zilebesiran is an investigational subcutaneously administered RNA interference therapeutic targeting hepatic AGT synthesis
- Phase 1 study data have demonstrated sustained reductions in serum AGT levels and blood pressure through 24 weeks after a single dose of zilebesiran in patients with mild to moderate hypertension[7]

Objective

- This additional part of the Phase 1 study investigated safety and pharmacology of sequential doses of zilebesiran in patients with hypertension and BMI of >35 to 50 kg/m^2

Zilebesiran Mediates Hepatic AGT Reduction



AGT, angiotensinogen; des(Ang1)AGT, des(Ang1)angiotensinogen; BMI, body mass index; GalNAc, N-acetylgalactosamine; RNA, ribonucleic acid; siRNA, small interfering ribonucleic acid.

1. Zhou B *et al*. *Nat Rev Cardiol*. 2021;18:785–802; 2. Danaei G *et al. PLoS Med*. 2009;6:e1000058; 3. Burnier M, Egan BM. *Circ Res*. 2019;124:1124–40; 4. Leggio M *et al. Hypertens Res*. 2017;40:947–63; 5. DeMarco VG *et al. Nat Rev Endocrinol*. 2014;10:364–476; 6. Erstad BL et al. *Am J Health-Sust Pharm.* 2022;79:1236–44; 7. Desai AS *et al. N Engl J Med*. 2023;389:228–38.

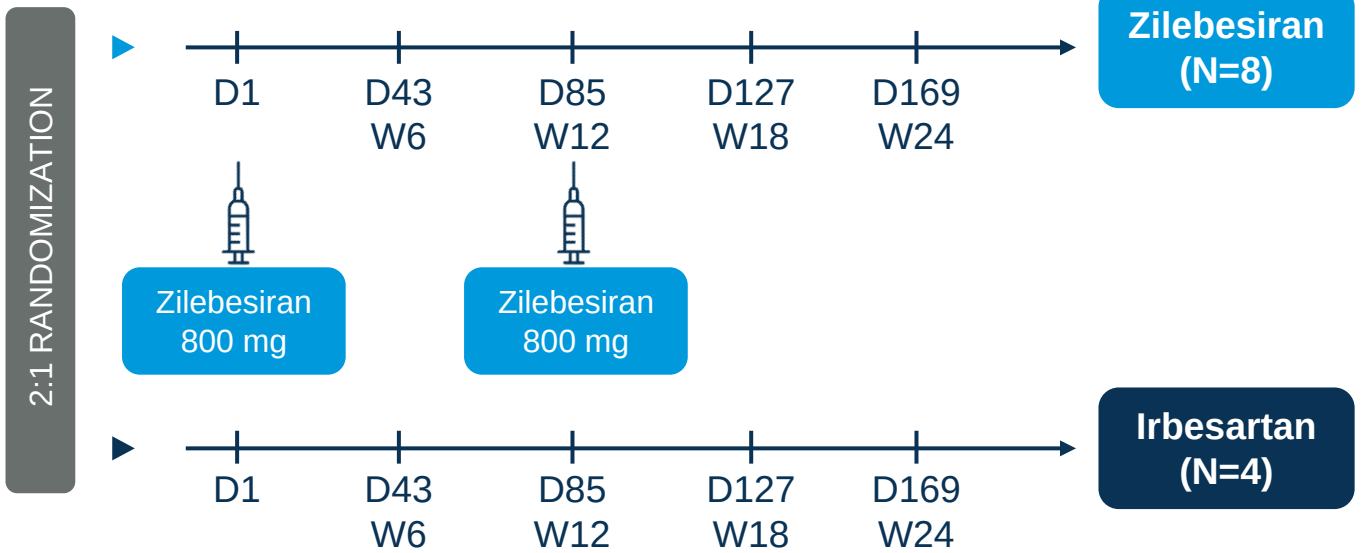
Phase 1 Part D Study Design

Randomized, Double-Blind, Double-Dummy Study to Assess Safety and Pharmacology of Sequential Doses of Zilebesiran in Patients with Class II or III Obesity

- A cohort of 12 patients was randomized 2:1 to receive zilebesiran (800 mg SC) or irbesartan (150 mg PO daily)
- Zilebesiran-treated patients received placebo PO daily
- Irbesartan-treated patients received two SC doses of saline (Day 1, Day 85)

Patient Population (N=12)

- 18–65 years of age
- BMI >35 kg/m^2 and ≤50 kg/m^2
- AOBP SBP >130 and ≤165 mmHg with no antihypertensives or after washout[a]
- Secondary hypertension[b] and diabetes mellitus[c] excluded



Primary Endpoint

- Frequency of AEs

Secondary Endpoints

- Change from baseline in serum AGT
- Plasma and urine single and multiple dose C_{max} and AUC of zilebesiran and potential metabolites

Key Exploratory Endpoints

- Change from baseline in SBP/DBP assessed by 24-hour ABPM
- Change from baseline in exploratory RAAS biomarkers

ClinicalTrials.gov registration number: NCT03934307. Class II obesity: BMI of >35 kg/m^2 to <40 kg/m^2, Class III obesity: BMI of ≥40 kg/m^2.

[a]Washout of ≥2 weeks or 4 weeks for long-acting antihypertensive medications such as chlorthalidone and long-acting calcium channel blockers. [b]Hypertension arising from an identifiable underlying primary cause. [c]Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or random plasma glucose ≥200 mg/dL (11.1 mmol/L) or HbA1c ≥6.5%.

ABPM, ambulatory blood pressure monitoring; AE, adverse event; AGT, angiotensinogen; AOBP, automated office blood pressure; AUC, area under the curve; BMI, body mass index; C_{max}, maximum plasma concentration; D, day; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; PO, oral; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SC, subcutaneous; W, week.

Baseline Demographics and Characteristics

Baseline Characteristics Were Generally Well Balanced Between Treatment Groups

Baseline Characteristics	Zilebesiran (N=8)	Irbesartan (N=4)	All Patients (N=12)
Median age, years (range)	54.0 (50–64)	58.0 (46–64)	55.5 (46–64)
Male, n (%)	3 (37.5)	1 (25)	4 (33.3)
Race, n (%)			
White	6 (75)	4 (100.0)	10 (83.3)
Asian	1 (12.5)	0 (0)	1 (8.3)
Black/African American	1 (12.5)	0 (0)	1 (8.3)
Mean BMI, kg/m^2 (SD)	40.4 (4.6)	38.9 (3.0)	39.9 (4.0)
24-hour mean SBP by ABPM, mmHg (SD)	143.1 (11.1)	144.3 (7.9)	143.5 (9.8)
24-hour mean DBP by ABPM, mmHg (SD)	87.4 (8.8)	87.8 (9.2)	87.5 (8.5)

ABPM, ambulatory blood pressure monitoring; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

Safety

Most Adverse Events Were Mild or Moderate in Severity and No Deaths Were Reported

Treatment-Emergent AEs, n (%)	Zilebesiran (N=8)	Irbesartan (N=4)
At least 1 AE	6 (75.0)	4 (100.0)
At least 1 SAE	1 (12.5)	0
At least 1 severe AE	1 (12.5)	0
At least 1 AE leading to study drug discontinuation	1 (12.5)	0
At least 1 AE leading to withdrawal from study during treatment period	1 (12.5)	0

- Headache was the only AE occurring in ≥2 patients (37.5%) following zilebesiran treatment
- A treatment-emergent SAE of an abnormal FibroScan® result occurred in a zilebesiran-treated patient[a]
  - The event was classified as serious, severe, and unrelated to study drug and led to study drug discontinuation
  - A repeat scan after the data cut-off suggested the patient had fatty liver
- One event of increase in ALT (3.5xULN) and one event of injection site reaction occurred in zilebesiran-treated patients
  - Both events were classified as mild, transient, and unrelated to study drug
- There were no episodes of hypotension requiring intervention in either arm

Based on data cut-off of April 20, 2022.

[a]The patient had an initial AE of moderate GGT increase, which triggered an ultrasound and the FibroScan® measurement. The scan measured a liver result suggestive of cirrhosis, though no clinical signs of cirrhosis were noted and cirrhosis was not formally diagnosed. The GGT increase was resolving without intervention at the time of data cut off. A repeat scan after LPLV showed no signs of liver fibrosis; the CAP score suggested a fatty liver instead. The outcome of the event was considered resolved/recovered with sequelae; investigation of the safety event took place after data cut-off.

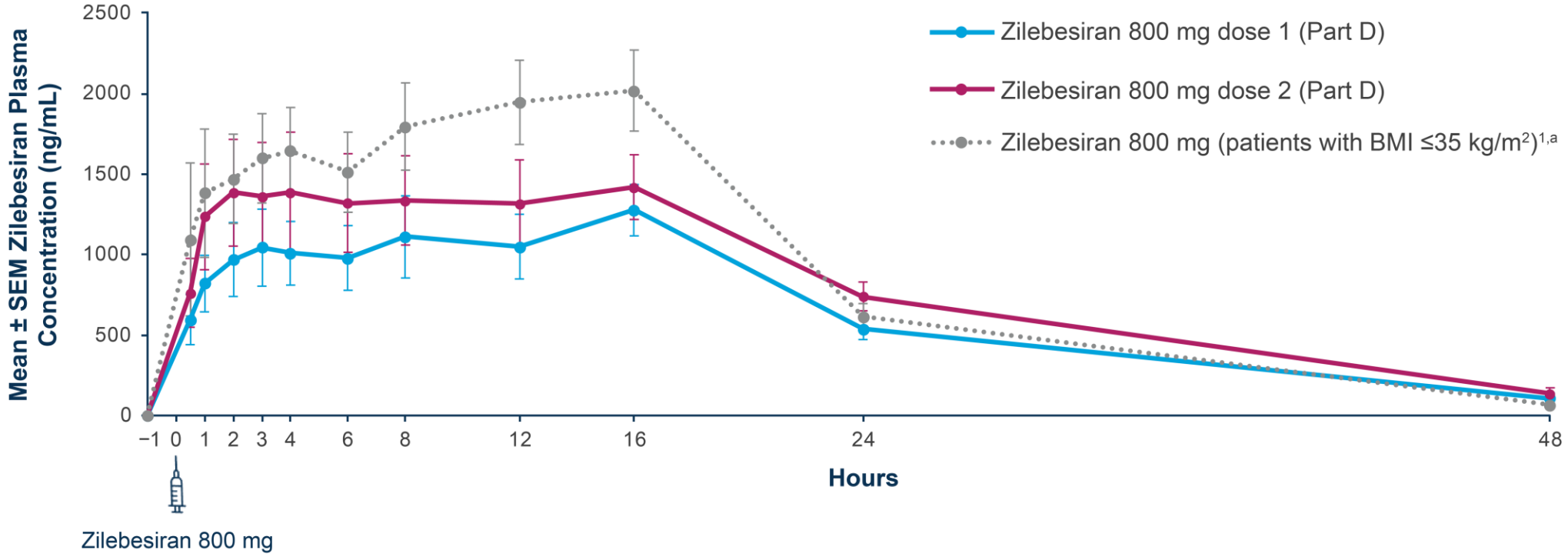
AE, adverse event; ALT, alanine aminotransferase; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; LPLV, last patient last visit; SAE, serious adverse event; ULN, upper limit of normal.

Plasma Zilebesiran Concentrations

Plasma Levels Declined by 24 Hours Post-Dose and Were Close to the LLOQ After 48 Hours

- Zilebesiran plasma concentrations were similar after dose 1 at Week 0 and dose 2 at Week 12, with no accumulation of study drug following the second dose
- Pharmacokinetic profile differences observed after a single dose of zilebesiran in patients with a BMI ≤35 kg/m^2 are expected but are not considered clinically relevant[1]

Plasma Zilebesiran Concentration-Time Profile

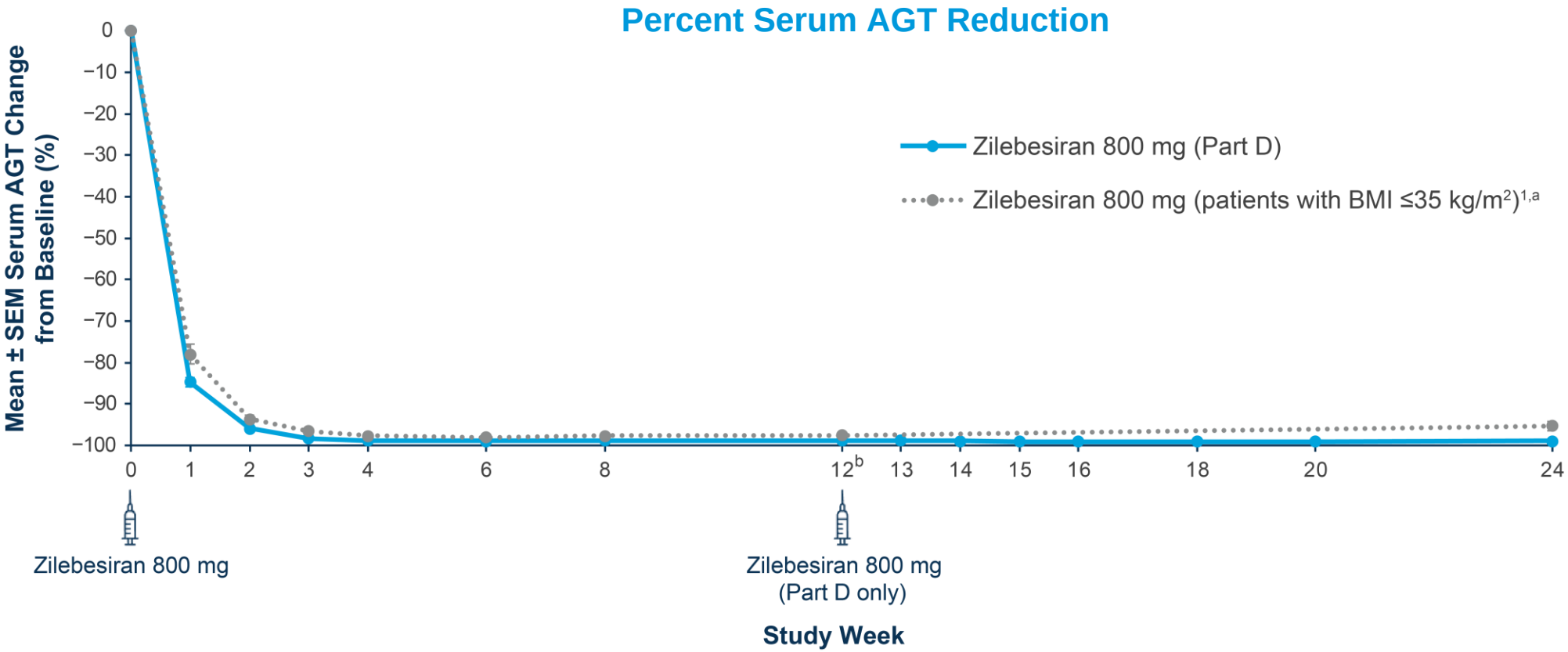


[a]Patients from Part A of the study; mean (SD) BMI of 28.6 kg/m^2 (3.92); comparisons between patients in Part A and Part D are indirect.
Based on data cut-off of April 20, 2022. Part A patient numbers: n=8. Part D patient numbers: dose 1 n=8, except Hour 16 (n=7); dose 2 n=6, except Hour –1 (n=4).
BMI, body mass index; LLOQ, lower limit of quantification; SD, standard deviation; SEM, standard error of the mean. 1. Desai AS *et al. N Engl J Med*. 2023;389:228–38.

Change From Baseline in Serum AGT

Sequential Doses of Zilebesiran 800 mg Led to Durable Reductions in Serum AGT Levels

- Following the first zilebesiran dose, mean serum AGT levels decreased by 96% at Week 2 and 99% at Week 4, which was sustained through to Week 24 following the second dose
- Reductions were comparable to those observed in patients with a BMI ≤35 kg/m^2 after a single dose of zilebesiran[1]



[a]Patients from Part A of the study; mean (SD) BMI of 28.6 kg/m^2 (3.92); comparisons between patients in Part A and Part D are indirect. [b]AGT measurements at Week 12 were taken on the day of the second dose of zilebesiran. Based on data cut-off of April 20, 2022. Serum AGT levels were measured using an enzyme-linked immunosorbent assay. Part A patient numbers: n=8, except Week 3 (n=7). Part D patient numbers: baseline–Week 1 n=8; Weeks 2–12 n=7; Weeks 13–24 n=6.

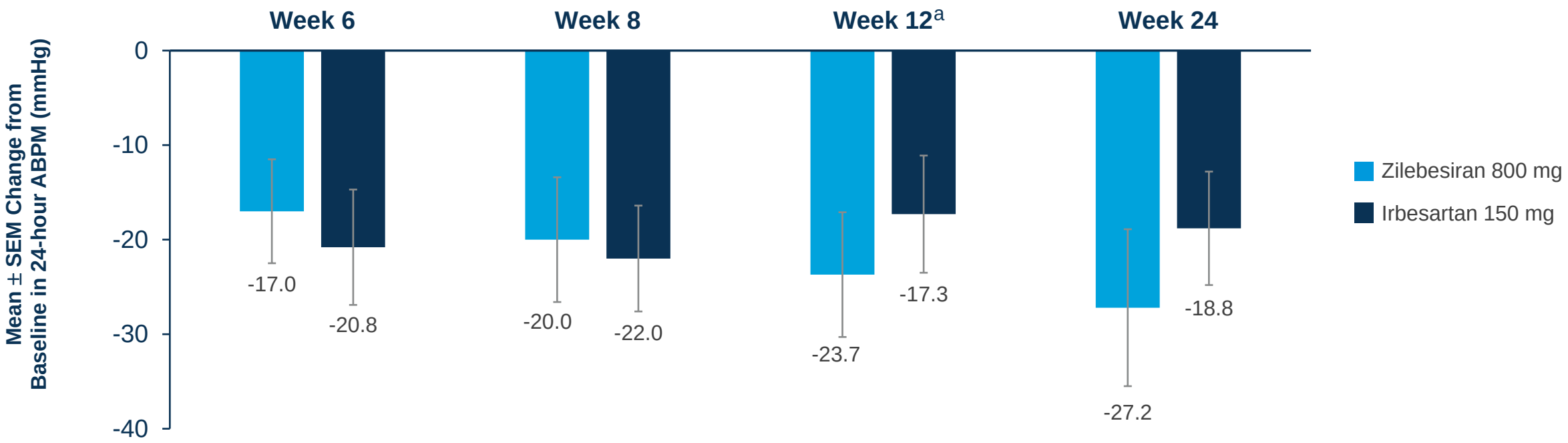
AGT, angiotensinogen; BMI, body mass index; SD, standard deviation; SEM, standard error of the mean. 1. Desai AS *et al. N Engl J Med*. 2023;389:228–38.

Change From Baseline in 24-Hour SBP

Sequential Doses of Zilebesiran 800 mg Led to Persistent Reductions in Blood Pressure

- Both zilebesiran and irbesartan reduced 24-hour mean SBP as measured by ABPM
- No add-on antihypertensives were required during the 24-week treatment period

Change from Baseline in 24-Hour Mean SBP



[a]SBP measurements at Week 12 were taken on the day before the second dose of zilebesiran

Based on data cut-off of April 20, 2022. Mean baseline SBP was 143.1 mmHg for zilebesiran and 144.3 mmHg for irbesartan. Zilebesiran patient numbers: baseline n=8; Weeks 6, 8, 12 n=7; Week 24 n=5. Irbesartan patient numbers: baseline–Week 24 n=4.

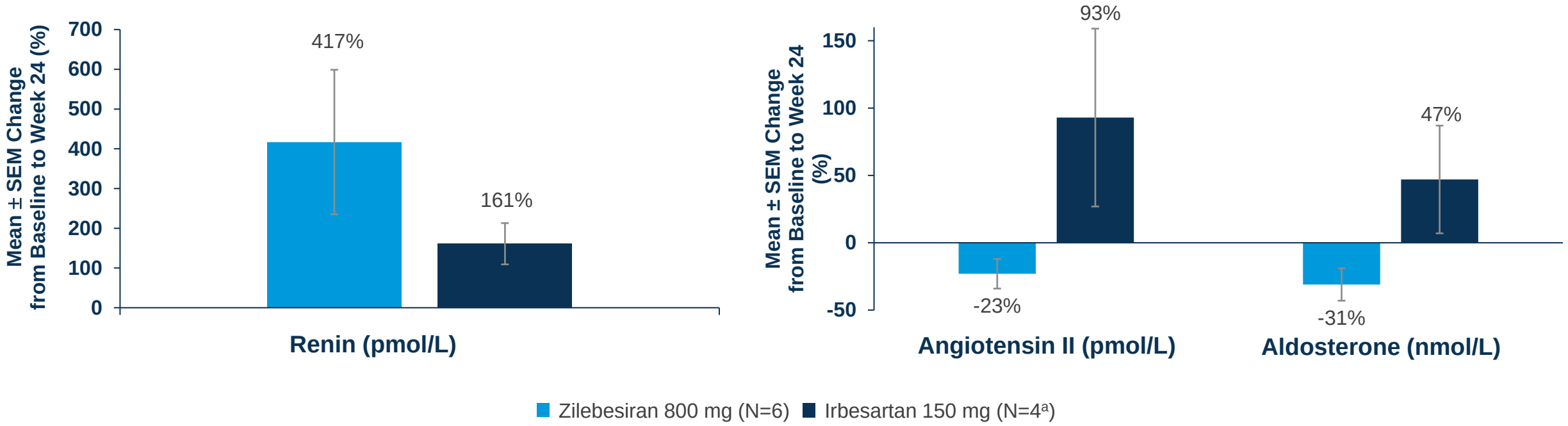
ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; SEM, standard error of the mean.

Change from Baseline in RAAS Biomarkers

Changes in RAAS Biomarker Levels Were Consistent With the MOA of Zilebesiran

- Both zilebesiran and irbesartan increased plasma renin concentration at Week 24; the greater elevation in plasma renin concentration with zilebesiran may reflect enhanced loss of the negative feedback inhibition of Ang II on renin secretion
- Zilebesiran was also associated with reductions in angiotensin II and aldosterone, while irbesartan increased levels of those biomarkers at Week 24

Change in Plasma RAAS Biomarker Concentration with Zilebesiran 800 mg and Irbesartan 150 mg at Week 24



Based on data cut-off of April 20, 2022.
Mean baseline plasma renin concentration: 0.16 pmol/L zilebesiran, 0.15 pmol/L irbesartan. Baseline Ang II: 3.63 pmol/L zilebesiran, 5.21 pmol/L irbesartan.
Baseline aldosterone: 0.35 nmol/L zilebesiran, 0.31 nmol/L irbesartan. [a]Aldosterone baseline and Week 24 for irbesartan: n=3.
MOA, mechanism of action; RAAS, renin-angiotensin-aldosterone system; SEM, standard error of the mean.

Conclusions

- Administration of sequential doses of zilebesiran 800 mg was generally well tolerated in patients with hypertension and BMI of >35 to 50 kg/m^2
- Plasma zilebesiran levels were close to the LLOQ after 48 hours and were accompanied by durable reductions in serum AGT through Week 24
- Persistent reductions in 24-hour mean SBP were observed with zilebesiran through to Week 24
- Zilebesiran increased plasma renin levels while reducing levels of angiotensin II and aldosterone, consistent with its mechanism of action
- These data build on results previously reported in a broader population of patients with hypertension[1] and suggest that the safety, pharmacodynamics, and BP-lowering effects of zilebesiran may be similar over a wide BMI range
- Zilebesiran is being further evaluated as a monotherapy or add-on therapy for treatment of hypertension in the ongoing KARDIA-1 (NCT04936035) and KARDIA-2 (NCT05103332) Phase 2 studies

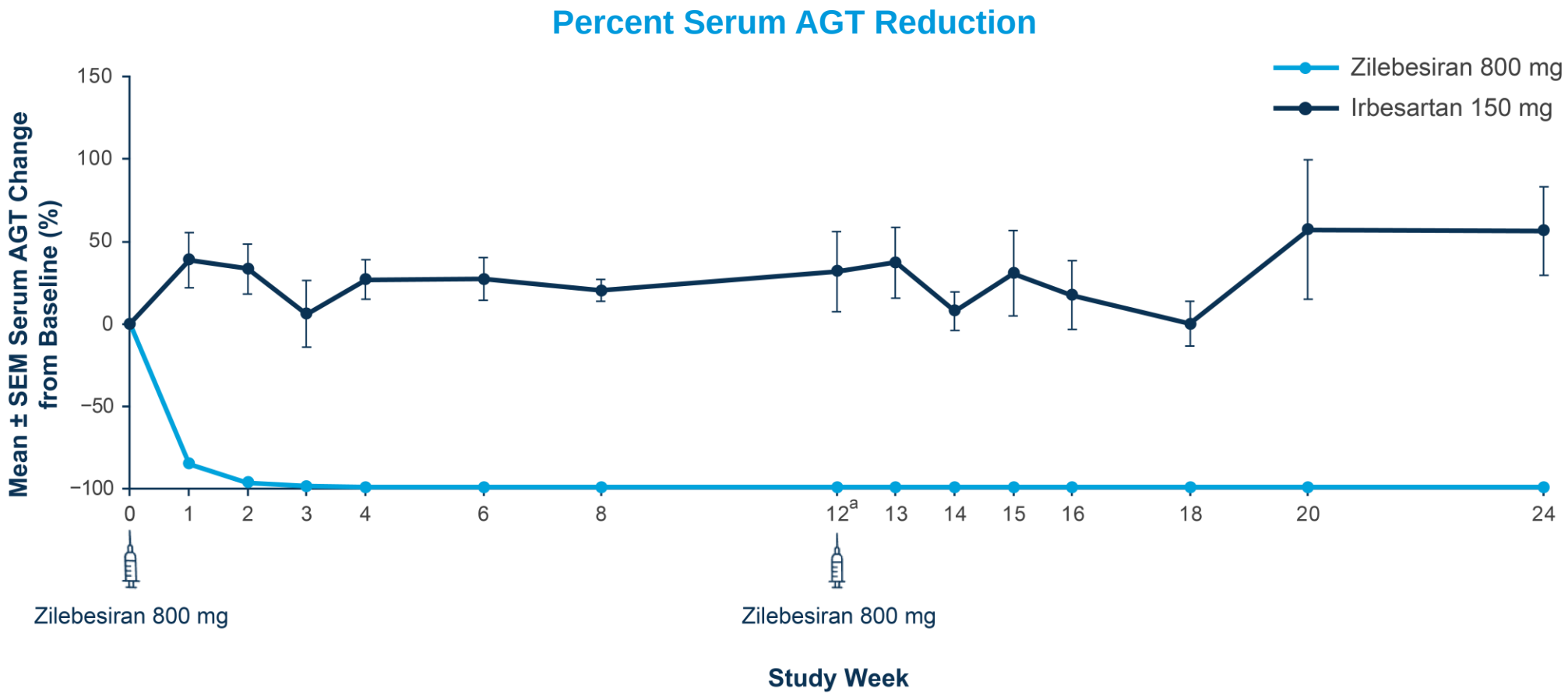
AGT, angiotensinogen; BMI, body mass index; BP, blood pressure; LLOQ, lower limit of quantification; SBP, systolic blood pressure.

1. Desai AS *et al. N Engl J Med*. 2023;389:228–38.

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the zilebesiran Phase 1 study

Back-Up Slides

Change From Baseline in Serum AGT with Irbesartan



[a]AGT measurements at Week 12 were taken on the day of the second dose of zilebesiran.

Based on data cut-off of April 20, 2022. Serum AGT levels were measured using an enzyme-linked immunosorbent assay. Zilebesiran patient numbers: baseline–Week 1 n=8; Weeks 2–12 n=7; Weeks 13–24 n=6; Week 36 n=4; Week 48 n=1. Irbesartan patient numbers: baseline–Week 24: n=4; Week 36: n=3.

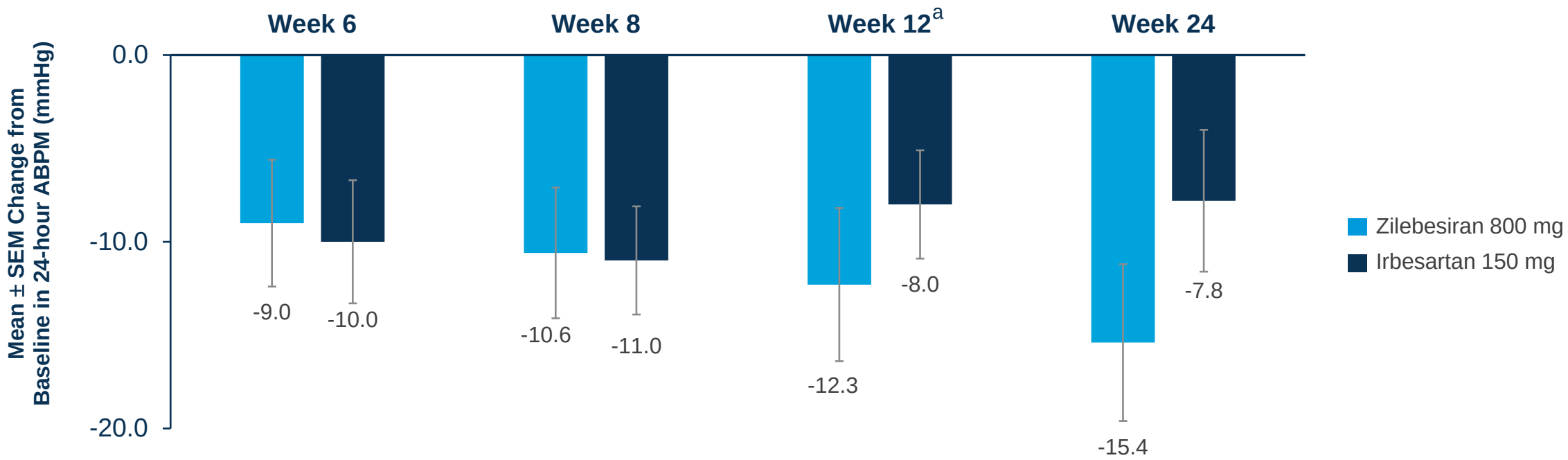
AGT, angiotensinogen; SEM, standard error of the mean.

Change From Baseline in 24-Hour DBP

Sequential Doses of Zilebesiran 800 mg Led to Persistent Reductions in Blood Pressure

- Both zilebesiran and irbesartan reduced 24-hour mean DBP as measured by ABPM

Change from Baseline in 24-Hour Mean DBP



[a]DBP measurements at Week 12 were taken on the day before the second dose of zilebesiran.

Based on data cut-off of April 20, 2022. Mean baseline DBP was 87.4 mmHg for zilebesiran and 87.8 mmHg for irbesartan. Zilebesiran patient numbers: baseline n=8, Weeks 6, 8, 12 n=7, Week 24 n=5. Irbesartan patient numbers: baseline–Week 24 n=4.

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SEM, standard error of the mean.