Zilebesiran: KARDIA-1 Study

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SUMMARY

- Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic designed to target hepatic synthesis of AGT and is currently being studied for the treatment of hypertension in adults.[1]
- KARDIA-1 was a phase 2 study to evaluate the safety and efficacy of zilebesiran dosing regimens for adults with mild to moderate hypertension. There were statistically significant decreases in both 24-h mean ambulatory SBP and office SBP measures across all zilebesiran regimens studied through Months 3 and 6.[1]
- AEs occurring in >5% of patients treated with zilebesiran were ISRs (6%, n=19/302) and hyperkalemia (5%, n=16/302), which were mild to moderate in severity and transient in nature.[1]

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STUDY DESIGN

The KARDIA-1 study (NCT04936035) was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging multicenter study to evaluate the efficacy and safety of zilebesiran in patients aged 18-75 years with mild-to-moderate hypertension (N=394). Patients included in the study had a daytime mean SBP ≥135 mmHg and ≤160 mmHg (evaluated through ABPM) without antihypertensive medication.[1]

The primary objective of the study was to evaluate the change in SBP from baseline to month 3, assessed by 24-hour ABPM.[1,2]

The secondary objectives of the study were to assess[1,2]:

- Change from baseline to month 3 in office SBP
- Change from baseline through month 6 in 24-hour mean SBP assessed by ABPM
- Change from baseline through month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction of ≥20 mmHg without additional antihypertensive medications at month 6 (from baseline through month 6)
- Time-adjusted change from baseline through month 6 in 24-hour mean SBP and DBP, assessed by ABPM
- Change from baseline through month 6 in 24-hour mean DBP
- Change from baseline through month 6 in office SBP and DBP
- Change in serum AGT from baseline through month 6

- Change from baseline through month 6 in daytime and nighttime SBP and DBP by ABPM (including Dipping Pattern)

Analyses were also conducted to assess the consistency of the zilebesiran treatment effect in various prespecified subgroups by the following baseline characteristics: age (<65 or ≥65 years), sex, race (Black or other), baseline 24-hour mean ambulatory SBP (<145 or ≥145 mmHg), and eGFR (<60 or ≥60 mL/min/1.73m^2).[1]

Exploratory objectives of the study evaluated the effect of zilebesiran over time on other measures of blood pressure reduction, such as the percentage of patients requiring rescue antihypertensives.[1,2]

Study participants received subcutaneous administration of either zilebesiran (150 mg q6m, 300 mg q6m, 300 mg q3m, or 600 mg q6m) or placebo for the first 6 months of the 12-month double-blind period. Patients previously taking antihypertensive medication must have been without antihypertensives for ≥2 weeks prior to randomization, and 4 weeks of washout were required for long-acting antihypertensive medications (eg, long-acting diuretics or calcium channel blockers).[1–3]

Participants randomized to placebo were re-randomized at month 6 to one of the 4 initial dosing regimens until the end of the 12-month double-blind treatment period. Participants originally randomized to zilebesiran regimens remained on their originally assigned treatment arm through the remainder of the study.[2] Patients could receive rescue antihypertensives at the discretion of the Investigator between months 3 and 5 and after month 6. Washout of rescue antihypertensives was required between months 5 and 6. Blood pressure measures were censored while patients were on or within 2 weeks after stopping a rescue antihypertensive.[3]

EFFICACY RESULTS

Patient Demographics and Baseline Characteristics

There were 394 patients randomized, with 377 patients included in the analysis set. Baseline demographics were balanced across study groups (**Table 1**).[1]

Table 1. Baseline Demographics and Disease Characteristics in KARDIA-1.[1,a]

	Zilebesiran				
	150 mg q6m (n=78)	**300 mg q6m (n=73)**	**300 mg q3m (n=75)**	**600 mg q6m (n=76)**	**Placebo (n=75)**
Mean age, years (SD)	55.5 (10.6)	56.4 (10.3)	57.7 (10.6)	57.4 (10.2)	56.8 (11.2)
Male sex, n (%)	39 (50)	44 (60)	45 (60)	45 (59)	37 (49)
Race, n (%)[b]					
American Indian or Alaska Native	1(1)	0	0	0	0
Asian	4 (5)	2 (3)	7 (9)	5 (7)	5 (7)
Black or African American	20 (26)	17 (23)	19 (25)	19 (25)	18 (24)
Native Hawaiian or Pacific Islander	0	0	1 (1)	0	0
White	53 (68)	54 (74)	48 (64)	52 (68)	52 (69)
Ethnicity, n (%)[b]					
Hispanic or Latino	19 (24)	16 (22)	10 (13)	20 (26)	9 (12)
BMI ≥30, n (%)	46 (59)	46 (63)	40 (53)	45 (59)	37 (49)
Type 2 diabetes, n (%)[c]	14 (18)	11 (15)	17 (23)	16 (21)	10 (13)
Receiving ≥1 hypertensive agent before study enrollment, n (%)[d]	43 (55)	55 (75)	57 (76)	63 (83)	55 (73)

	Zilebesiran				Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	600 mg q6m (n=76)	
24-hour ambulatory SBP/DBP, mean (SD), mmHg	141 (9)/ 82 (8)	143 (9)/ 82 (9)	142 (8)/ 82 (9)	143 (9)/ 81 (8)	141 (8)/ 82 (8)
Office SBP/DBP, mean (SD), mmHg	142 (11)/ 87 (10)	143 (11)/ 89 (9)	140 (11)/ 85 (9)	141 (11)/ 86 (9)	143 (13)/ 88 (11)
eGFR ≥60 mL/min/1.73m^2, n (%)	68 (87)	70 (96)	69 (92)	68 (90)	64 (85)
Serum angiotensinogen concentration, mean (SD), ng/mL	22.1 (5.9)	23.2 (7.8)	20.8 (4.9)	21.7 (5.9)	23.9 (10.9)

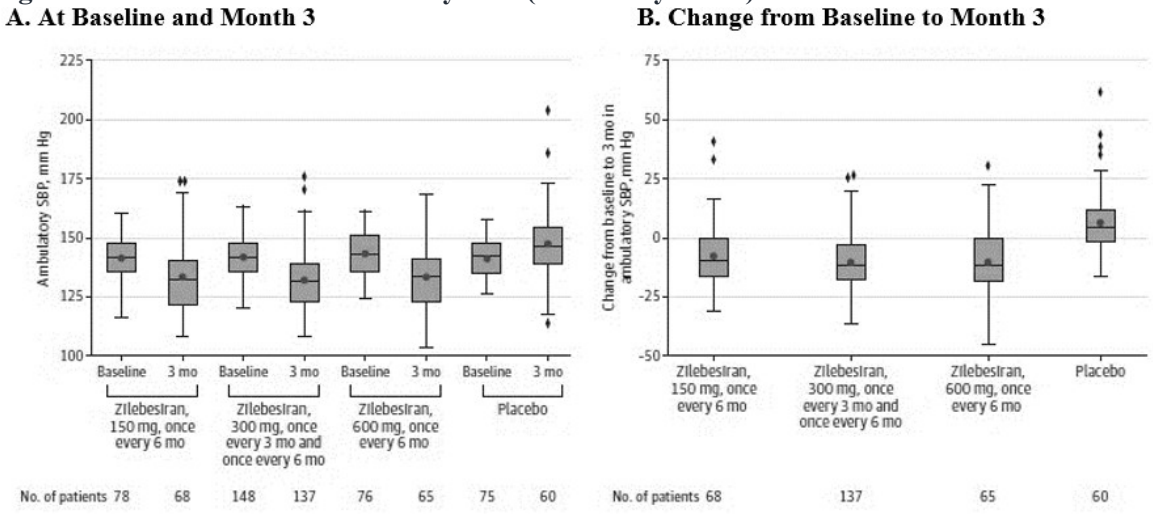
Abbreviations: BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; q3m = every 3 months; q6m = every 6 months; SBP = systolic blood pressure; SD = standard deviation.
[a]All randomized patients who received any amount of study drug. Patients enrolled at sites in Ukraine (n = 16) were excluded from the analysis populations. [b]Race and ethnicity were self-reported from patient to the investigator in closed categories. For ethnicity, categories were Hispanic or Latino, not Hispanic or Latino, not reported, or unknown. For race, categories were American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other (please specify), or not reported. [c]Patients who met the study inclusion criteria with at least 1 of the following: medical history of type 2 diabetes, glycated hemoglobin A1c >7% before first study drug dose, or taking diabetes medication before first study drug dose. [d]Safety analysis set included all patients who received any amount of study drug, grouped according to the treatment actually received.

Systolic Blood Pressure

At month 3, the LSM differences in the change from baseline in 24-hour mean ambulatory SBP between zilebesiran and placebo were −14.1 mmHg (95% CI, −19.2 to −9.0) for zilebesiran 150 mg every 6 months; −16.7 mmHg (95% CI, −21.2 to −12.3) for zilebesiran 300 mg every 3 months or every 6 months; and −15.7 mmHg (95% CI, −20.8 to −10.6) for zilebesiran 600 mg every 6 months.[1]

There were statistically significant (p-value <.001) decreases from baseline to month 3 in 24-hour mean ambulatory SBP across all zilebesiran regimens studied (**Figure 1**) as well as from baseline to month 6 (**Table 2**). Similar changes from baseline and differences vs placebo were observed at months 3 and 6 for office SBP (**Table 2**).[1]

Figure 1. 24-Hour Mean Ambulatory SBP (Full Analysis Set).[1]



Adapted from Bakris et al[1]
Abbreviations: mo = month; no = number; SBP = systolic blood pressure.

Table 2. Change from Baseline to Month 3 or 6 in 24-Hour Mean Ambulatory and Office SBP (Full Analysis Set).[1,a,b]

Outcome	Zilebesiran					Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	300 mg q6m or q3m (n=148)	600 mg q6m (n=76)	
Office SBP at month 3, mmHg	131.8 (13.6) [n=68]	–	–	129.1 (13.8) [n=134]	131.1 (15.9) [n=64]	141.4 (12.6) [n=60]
LSM change from baseline (95% CI), mmHg	-9.7 (-12.6 to -6.8)	–	–	-12.1 (-14.2 to -10.0) [n=133]	-9.2 (-12.1 to -6.2)	-0.1 (-3.2 to 3.0)
LSMD vs placebo (95% CI), mmHg[b]	-9.6 (-13.8 to -5.3)	–	–	-12.0 (-15.7 to -8.3) [n=133]	-9.1 (-13.4 to -4.8)	–
P-value	<.001	–	–	<.001	<.001	–
Ambulatory SBP at month 6, mmHg	134.4 (15.0) [n=62]	132.2 (13.8) [n=68]	131.6 (12.2) [n=60]	–	131.7 (16.8) [n=63]	144.6 (15.0) [n=54]
LSM change from baseline (95% CI), mmHg	-6.5 (-9.7 to -3.3)	-9.9 (-13.0 to -6.8)	-9.5 (-12.8 to -6.3)	–	-9.6 (-12.8 to -6.4)	4.6 (1.2 to 8.0)
LSMD vs placebo, mmHg[b]	-11.1 (-15.8 to -6.4)	-14.5 (-19.1 to -9.9)	-14.1 (-18.9 to -9.4)	–	-14.2 (-18.9 to -9.5)	–
P-value	<.001	<.001	<.001	–	<.001	–
Office SBP at month 6, mmHg	133.7 (13.6) [n=65]	131.2 (16.1) [n=68]	127.4 (14.5) [n=58]	–	128.9 (15.6) [n=62]	140.6 (12.4) [n=57]
LSM change from baseline (95% CI), mmHg	-8.2 (-11.5 to -4.8)	-11.1 (-14.4 to -7.8)	-12.8 (-16.3 to -9.2) [n=57]	–	-10.8 (-14.2 to -7.4)	-0.6 (-4.2 to 2.9)
LSMD vs placebo (95% CI), mmHg[b]	-7.5 (-12.4 to -2.7)	-10.5 (-15.3 to -5.7)	-12.1 (-17.2 to -7.1) [n=57]	–	-10.2 (-15.1 to -5.3)	–
P-value	.003	<.001	<.001	–	<.001	–

Abbreviations: LSM = least-squares mean; LSMD = least-squares mean difference; q3m = every 3 months; q6m = every 6 months; SBP = systolic blood pressure.

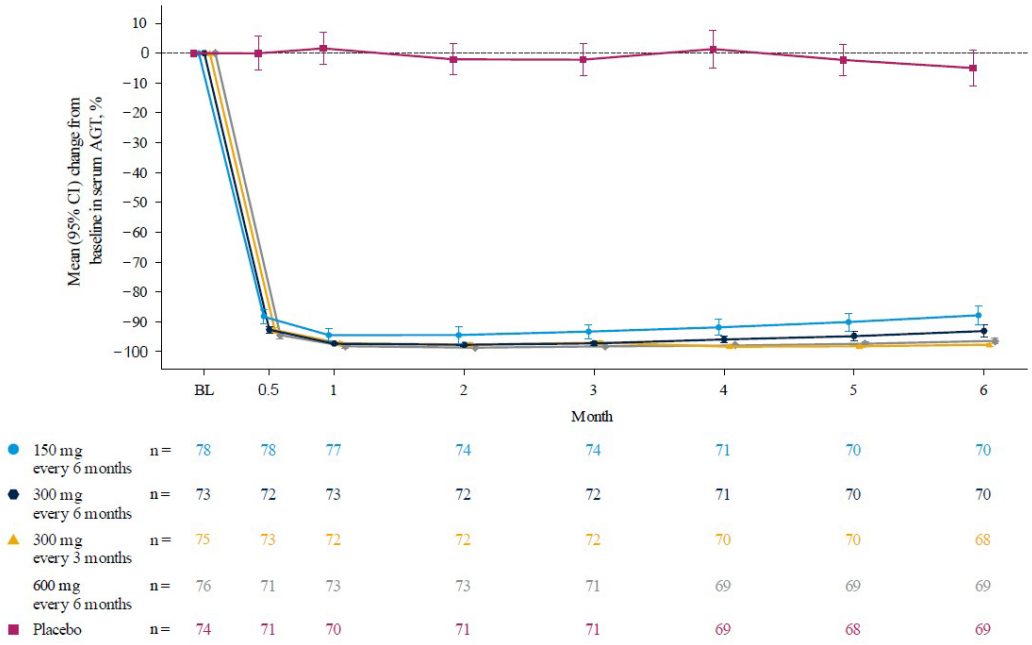
[a]All randomized patients who received any amount of study drug, analyzed according to randomized treatment. [b]Mixed model for repeated measures adjusted for race and corresponding baseline SBP. P values and 95% CIs for the primary endpoint are adjusted based on the Dunnett test.

At months 3 and 6, reductions from baseline SBP were consistent for each hour of the 24-hour diurnal cycle in zilebesiran-treated patients and were greater in magnitude than placebo across all zilebesiran regimens studied.[1]

Serum Angiotensinogen

The change from baseline to months 3 and 6 in serum angiotensinogen was greater in patients receiving any dose of zilebesiran than those who received placebo. (**Figure 2**). After single 300 mg or 600 mg doses of zilebesiran, a decrease greater than 90% was observed and persisted to month 6.[1]

Figure 2. Mean Percent Change from Baseline in Serum AGT.[3]



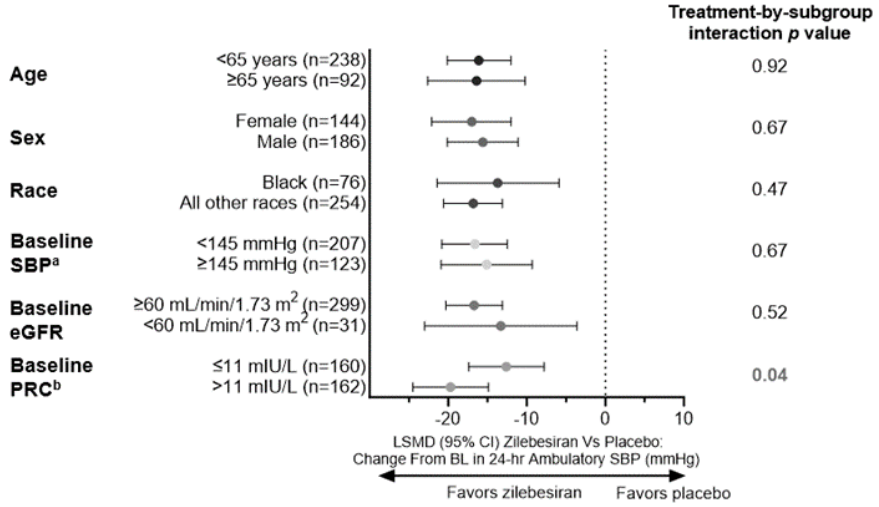
Adapted from Bakris et al[1]
Abbreviations: AGT = angiotensinogen; BL = baseline; CI = confidence interval; Data points are staggered for visualization.

Subgroup Analysis

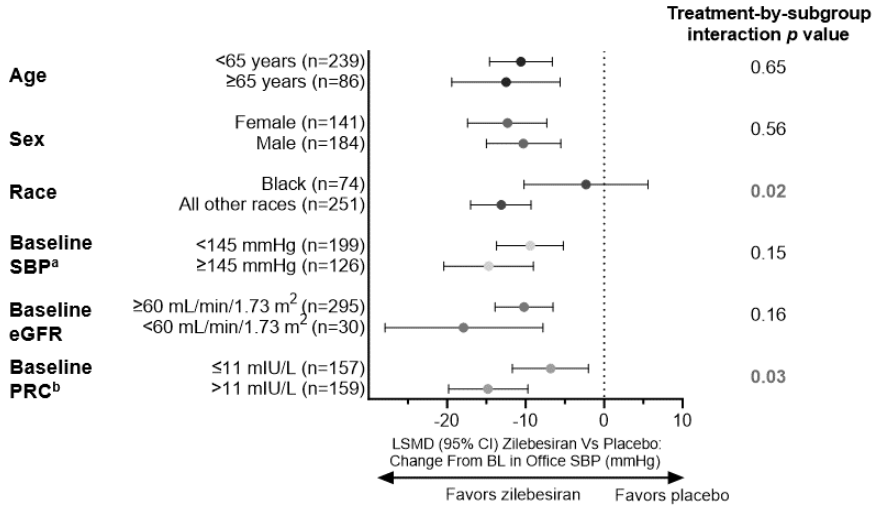
At month 3, the ambulatory SBP reductions were generally consistent across subgroups (**Figure 3**).[4] A variation in SBP reduction was observed in race subgroup, in which Black patients experienced lower SBP reduction compared to patients of all other races. Post hoc analysis of the subgroup defined by baseline PRC identified that this racial variation was largely attributed to the low baseline PRC in Black patients (median of 5.2 mIU/L) compared to the PRC level (median of 13.5 mIU/L) in patients of all other races. Patients with higher baseline PRC had greater mean reductions across both 24-h mean ambulatory SBP and office SBP measures (**Table 3**).[4]

Figure 3. LSMD (95% CI) for Zilebesiran (All Doses Combined) vs Placebo.[4]

A. Change from Baseline to Month 3 in 24-Hour Mean Ambulatory SBP



B. Change from Baseline to Month 3 in Mean Office SBP



Adapted from Saxena et al[4]
Abbreviations: BL = baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; hr = hours; LSMD = least-square mean difference; PRC = plasma renin concentration; SBP = systolic blood pressure.

Table 3. LSM Change from Baseline to Month 3 in SBP by PRC and Race Subgroups.[4]

Race	Baseline PRC Above or Below Median (11 mIU/L)	Zilebesiran (all doses combined)	
		24-hr Mean Ambulatory SBP (SE)	Office SBP (SE)
Black	≤ 11 mIU/L (n=52)	-0.7 (2.1)	-2.7 (2.0)
Median PRC: 5.2 mIU/L	>11 mIU/L (n=17)	-12.1 (3.0)	-13.4 (2.5)
All other races	≤11 mIU/L (n=96)	-8.3 (1.2)	-10.9 (1.2)
Median PRC: 13.5 mIU/L	>11 mIU/L (n=129)	-12.6 (1.1)	-13.7 (1.1)

Abbreviations: LSM = least-squares mean; PRC = plasma renin concentration; SBP = systolic blood pressure; SE = standard error.
Placebo data not presented owing to small sample size.

Exploratory Analysis

Patients Requiring Rescue Antihypertensives

During the 6-month double-blind treatment period, a higher percentage of patients in the placebo arm required rescue antihypertensives (52.0%) compared to patients in the zilebesiran arms (20.5%–32.1%). In all study arms, the most frequently prescribed classes of rescue antihypertensives were calcium channel blockers and diuretics.[1]

SAFETY RESULTS

Drug-related AEs reported in >5% of patients treated with zilebesiran included ISRs (n=19/302, 6.3%) and hyperkalemia (n=16/302, 5.3%); all of these events were mild to moderate in severity and transient in nature. (**Table 4**). Serious AEs were reported in 5 patients (6.7%) in the placebo group and 11 patients (3.6%) in the zilebesiran groups, none of which were considered related to the study drug. There were 3 patients with drug-related AEs leading to dose interruption and 4 patients with drug-related AEs leading to discontinuation (orthostatic hypotension [n=2], BP elevation [n=1], and injection site reaction [n=1]).[1]

Among the treatment-emergent AEs of clinical interest, 1 event of AKI was reported in the zilebesiran 300 mg every 3 months arm, which was considered unrelated to zilebesiran. There were no serious hepatic AEs, and the majority of LFT elevations were transient and resolved while receiving treatment. Hypotension AEs were mild or moderate in severity and transient in nature, with one event in zilebesiran 300 mg every 3 months group requiring treatment with normal saline. Hyperkalemia AEs were mild and did not lead to acute kidney injury or study drug discontinuation.[1]

Table 4. Summary of AEs During the 6-Month Double-Blind Treatment Period.[1,a]

AE, n (%)	Zilebesiran				Zilebesiran Total (N=302)	Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	600 mg q6m (n=76)		
At least 1 AE	45 (58)	44 (60)	46 (61)	49 (64)	184 (61)	38 (51)
Related to study drug[b]	12 (15)	12 (16)	14 (19)	13 (17)	51 (17)	6 (8)
At least 1 SAE[c]	0	1 (1)	4 (5)	6 (8)	11 (4)	5 (7)
Related to study drug[b]	0	0	0	0	0	0
At least 1 study drug-related AE leading to study drug interruption[b,d]	1 (1)	0	1 (1)	1 (1)	3 (1)	0
At least 1 study drug-related AE leading to study drug discontinuation[b,e]	1 (1)	1 (1)	1 (1)	1 (1)	4 (1)	0
Death	0	0	1 (1)	0	1 (<1)	0
Study drug-related AEs occurring in at least 5% of patients[b]						
Hyperkalemia	4 (5)	3 (4)	4 (5)	5 (7)	16 (5)	1 (1)
ISR	3 (4)	4 (5)	8 (11)	4 (5)	19 (6)	0
Additional treatment-emergent AE of clinical interest (any relatedness)						
Potential hypotension[f]	6 (8)	6 (8)	5 (7)	7 (9)	24 (8)	5 (7)
Hyperkalemia[g]	5 (6)	4 (5)	5 (7)	5 (7)	19 (6)	2 (3)
Hypotension[h]	3 (4)	3 (4)	3 (4)	4 (5)	13 (4)	1 (1)

AE, n (%)	Zilebesiran				Zilebesiran Total (N=302)	Placebo (n=75)
	150 mg q6m (n=78)	300 mg q6m (n=73)	300 mg q3m (n=75)	600 mg q6m (n=76)		
Hepatic AE[i]	2 (3)	2 (3)	4 (5)	1 (1)	9 (3)	1 (1)
Acute kidney failure[j]	1 (1)	1 (1)	1 (1)	1 (1)	4 (1)	0

Abbreviations: AE = adverse event; AKI = acute kidney injury; BP = blood pressure; ISR = injection site reaction; MedDRA = Medical Dictionary for Regulatory Activities; q3M = every 3 months; q6M = every 6 months; SAE = serious adverse event; SMQ = Standardized MedDRA Query.

[a]AEs are defined per MedDRA terminology. [b]Related to study drug indicates a reasonable possibility that the event may have been caused by the study drug as evaluated by the investigator. [c]SAEs are any untoward medical occurrence that, at any dose, results in death; is life-threatening (an event that places the patient at immediate risk of death from the event as it occurred but does not include an event that had it occurred in a more severe form might have caused death); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above. [d]Study drug interruption refers to a pause of further study drug dosing (including placebo dosing) with potential to resume. [e]Study drug discontinuation is the stopping of further study drug dosing (including placebo dosing) without potential to resume. [f]Include decreased blood pressure, hypotension, orthostatic hypotension, dizziness, syncope, and orthostasis. [g]Include hyperkalemia, increased serum potassium, and abnormal serum potassium. [h]Include additional terms of decreased blood pressure, hypotension, and orthostatic hypotension. [i]Include AEs mapped to the standardized MedDRA query drug-related hepatic disorders, both narrow and broad terms. Terms include but are not limited to alanine aminotransferase increased; aspartate aminotransferase increased; serum alkaline phosphatase increased; serum bilirubin increased; gamma-glutamyltransferase increased; liver function test abnormal; liver function test increased; and transaminases increased. [j]Acute kidney failure includes events of increased serum creatinine, increased blood urea, decreased glomerular filtration rate, and acute kidney injury.

ABBREVIATIONS

AE = adverse event; ABPM = ambulatory blood pressure monitoring; AGT = angiotensinogen; AKI = acute kidney injury; BL = baseline; BP = blood pressure; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; hr = hours; ISR = injection site reaction; LSM = least-squares mean; LSMD = least-squares mean difference; mo = month; MedDRA = Medical Dictionary for Regulatory Activities; no = number; PRC = plasma renin concentration; RNAi = RNA interference; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; SMQ = Standardized MedDRA Query; q3m = every 3 months; q6m = every 6 months.

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