Zilebesiran: Phase 1 Study Overview

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The safety and efficacy of zilebesiran are currently being investigated in clinical studies and has not been evaluated by the FDA or any health authority.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Zilebesiran is an investigational subcutaneously administered RNAi therapeutic designed to reduce circulating AGT protein, leading to reduction in blood pressure. Zilebesiran is currently being studied for the treatment of hypertension in adults. Zilebesiran utilizes GalNAc conjugation, which enables subcutaneous dosing for liver-specific silencing of AGT mRNA.[1]
- The Phase 1 study was a 4-part, multicenter phase 1 study designed to assess the safety, PK, and PD characteristics, as well as exploratory antihypertensive efficacy with 24-hour ABPM in patients with hypertension.[1]
    - Parts A and B were randomized, double-blind, placebo-controlled studies of a single ascending dose (Part A) and a single fixed dose during low- and high-salt diet conditions (Part B). Part C was removed during a protocol amendment. Part D was a randomized, double-blind, double-dummy study of two sequential doses of zilebesiran in patients with class II or III obesity. Part E was an open-label study of a single fixed dose of zilebesiran with daily irbesartan coadministration.[1,2]
    - The majority of AEs reported across the study subsections were mild or moderate in severity, and there were no reports of hypotension requiring intervention.[1,2]
    - In Parts A, B, and E, dose-dependent reductions in both serum AGT levels and 24-hour ABPM were maintained for up to 24 weeks following a single dose of zilebesiran. In Part D, reductions in 24-hour mean SBP were observed with 2 sequential doses of 800 mg of zilebesiran for up to 24 weeks in patients with obesity.[1,2]

INDEX

STUDY DESIGN

The Phase 1 study was a 4-part, multicenter phase 1 study designed to assess the safety, PK, and PD characteristics of zilebesiran, as well as exploratory antihypertensive efficacy with 24-hour ABPM in patients with hypertension. In Parts A, B, and E, adult patients (aged 18 to 65) were eligible to participate if they a had a mean seated SBP as assessed by automated cuff of more than 130 to 165 mmHg (in Parts A and B) or more than 135 to 165 mmHg (in Part E), and a mean SBP of 130 mmHg or more as

assessed by 24-hour ABPM, following washout of antihypertensive medications for at least 2 weeks. Patients with secondary hypertension, postural hypotension, diabetes, previous CV events, and current or anticipated treatment with β-adrenergic receptor-blocked drugs were excluded from the study.[1] In Part D, adult patients aged 18 to 65 were eligible to participate if they had an automated office SBP greater than 130 to 165 mmHg with no antihypertensive medications, or following washout of antihypertensive medications (for ≥2 weeks or 4 weeks for long-acting antihypertensive medications such as chlorthalidone and long-acting calcium channel blockers). Patients included in Part D had a BMI >35 to 50 kg/m^2.[2]

There were 119 patients enrolled in the Phase 1 study:[1,2]

- In **Part A**, 84 eligible patients were randomly assigned in a 2:1 ratio to receive a single SC dose of zilebesiran (10, 25, 50, 100, 200, 400, or 800 mg; N=56) or placebo (N=28). Add-on hypertensive treatment was permissible at the discretion of the Investigator at 8 weeks, if needed for uncontrolled hypertension.[1]
  - The primary objective of Part A was to evaluate the safety and pharmacology of a single dose of zilebesiran in patients with hypertension.
- In **Part B**, following sequential implementation of a low-salt diet (0.23 g/day) and a high-salt diet (5.75 g/day) from days -21 through -8, 12 patients were randomly assigned in a 2:1 ratio to receive a single 800 mg dose of zilebesiran (N=8), or placebo (N=4). Patients were rechallenged with the same dietary protocol (low-salt to high-salt) from days 43 through 56, corresponding to the timing of the expected peak effect of zilebesiran.[1]
  - The primary objective of Part B was to evaluate how the intake of dietary salt could influence the blood-pressure lowering effects of zilebesiran.
- In **Part D**, 12 eligible patients were randomly assigned in a 2:1 ratio to receive zilebesiran 800 mg SC (study day 1 and day 85; N=8) or irbesartan 150 mg PO daily (N=4). In order to maintain blinding, both treatment arms received either placebo PO daily or 2 SC doses of saline (study day 1 and day 85).[2]
  - The primary objective of Part D was to evaluate the safety and pharmacology of sequential doses of zilebesiran in patients with hypertension and BMI >35 to 50 kg/m^2.
- In **Part E**, all 16 patients received a single 800 mg dose of zilebesiran. In patients with a SBP of 120 mmHg or more at week 6 (as assessed by ABPM), additional treatment with irbesartan 300 mg once daily for 2 weeks was administered.[1]
  - The primary objective of Part E was to evaluate the safety and pharmacology of a single dose of zilebesiran co-administered with irbesartan.

Following the conclusion of the 12-week treatment period for Parts A, B, and E, patients entered an extended safety follow-up period. All patients were given guidance regarding limiting alcohol intake, avoiding supplements impacting BP, and restricting dietary salt intake to 2.0 g/day during the duration of the study (except as indicated for participants in Part B).[1]

Study Endpoints

Primary Endpoint

The primary endpoint was the frequency of AEs.[1,2]

Secondary Endpoints

The secondary endpoints were the change from baseline in the serum AGT level and the PK characteristics of zilebesiran.[1,2]

Select Exploratory Endpoints

Select exploratory endpoints included[1,2]:

- Changes from baseline in SBP and DBP as measured by 24-hour ABPM at weeks 6, 8, 12, and 24 in Part A of the study.
- Changes from baseline in SBP and DBP as measured by 24-hour ABPM during low and high-salt intake before and after dose administration in Part B of the study.
- Changes from baseline in SBP and DBP as measured by 24-hour ABPM and change from baseline in exploratory RAAS biomarkers in Part D of the study.
- Changes from baseline in SBP and DBP as measured by 24-hour ABPM before and after daily irbesartan coadministration in Part E.

Patient Demographics & Baseline Characteristics

Baseline characteristics of participants enrolled in Parts A, B, and E and of participants enrolled in Part D are summarized in **Table 1** and **Table 2,** respectively.[1,2]

Table 1. Baseline Demographic and Clinical Characteristics of Patients in Parts A, B, and E.[1]

Characteristic	Part A		Part B		Part E[a]		All Patients (N=107)[b]
	Placebo (N=28)	All Zilebesiran (N=56)	Placebo (N=4)	Zilebesiran (N=8)	Zilebesiran (N=6)	Zilebesiran & Irbesartan (N=10)	
Mean age (range), yr	52.9 (36-64)	53.0 (35-65)	50.0 (35-62)	59.0 (49-64)	54.0 (44-58)	55.2 (42-64)	53.5 (35-65)
Male sex, n (%)	16 (57)	35 (62)	3 (75)	6 (75)	5 (83)	3 (30)	66 (62)
Race, n (%)[c]							
White	21 (75)	35 (62)	3 (75)	5 (62)	6 (100)	4 (40)	71 (66)
Black	6 (21)	16 (29)	1 (25)	2 (25)	0	3 (30)	27 (25)
Asian	0	3 (5)	0	1 (12)	0	1 (10)	5 (5)
Other	1 (4)	2 (4)	0	0	0	2 (20)	4 (4)
BP, mmHg[d]							
SBP	140.6 ± 8.3	139.2 ± 9.4	148.5 ± 2.6	139.0 ± 7.4	133.0 ± 6.6	147.0 ± 7.5	140.3 ± 9.0
DBP	87.9 ± 7.9	85.8 ± 6.8	99.0 ± 2.8	86.4 ± 6.3	85.8 ± 8.0	89.0 ± 6.3	87.1 ± 7.3
BMI[e]	29.3 ± 3.1	28.6 ± 3.0	29.3 ± 2.0	29.0 ± 4.3	29.7 ±3.6	28.3 ± 4.7	28.7 ± 3.2

Abbreviations: ABPM = ambulatory blood pressure monitoring; BMI = body-mass index; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Plus-minus values are means ±SD. Percentages may not total 100 due to rounding.

[a]Part E was a single-group study, with all patients receiving a single 800-mg dose of zilebesiran. Patients with a SBP of 120 mmHg or more at week 6 as assessed by 24-hour ABPM received additional treatment with irbesartan at a dose of 300 mg once daily for 2 weeks and are shown in the zilebesiran & irbesartan column.

[b]Five patients from Part A participated in Part E.

[c]Race was self-reported by patients.

[d]Shown are mean-24-hour BP levels as assessed by ABPM.

[e]The BMI is the weight in kilograms divided by the square of the height in meters

Table 2. Baseline Demographic and Clinical Characteristics of Patients in Part D.[2]

Characteristic	Part D		All Patients (N=12)
	Zilebesiran (N=8)	Irbesartan (N=4)	
Median age (range), yr	54.0 (50-64)	58.0 (46-64)	55.5 (46-64)
Male sex, n (%)	3 (37.5)	1 (25)	4 (33.3)
Race, n (%)[§]			
White	6 (75)	4 (100)	10 (83.3)
Black	1 (12.5)	0	1 (8.3)
Asian	1 (12.5)	0	1 (8.3)
24-hour mean BP, mmHg ± SD			
24-hour mean SBP by ABPM	143.1 ± 11.1	144.3 ± 7.9	143.5 ± 9.8
24-hour mean DBP by ABPM	87.4 ± 8.8	87.8 ± 9.2	87.5 ± 8.5
Mean BMI, kg/m^2 ± SD	40.4 ± 4.6	38.9 ± 3.0	39.9 ± 4.0

Abbreviations: ABPM = ambulatory blood pressure monitoring; BMI = body-mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.

SAFETY RESULTS

A summary of AEs across Parts A, B, and E is shown in **Table 3**. In the pooled population, AEs were reported in a total of 86 patients (58/80, 72% of patients that received zilebesiran and 28/32, 88% of patients that received placebo). AEs reported in at least 5% of the pooled patient population were headache, ISR, and URTI; most of which were mild or moderate. ISRs were the only treatment-related AE reported in more than 2 patients. There were 3 serious AEs that occurred: ischemic optic neuropathy in a patient randomized to placebo in Part A; prostate cancer resulting in surgery in a patient receiving 200 mg of zilebesiran in Part A; and acute anemia due to a complication of a procedure conducted during screening (prior to receipt of zilebesiran) in a patient receiving zilebesiran and irbesartan in Part E.[1]

Table 3. Summary of AEs in Parts A, B, and E.[1]

Event, n (%)	Part A		Part B		Part E		Pooled Parts A, B, and E	
	Placebo (N=28)	All Zilebesiran (N=56)	Placebo (N=4)	Zilebesiran (N=8)	Zilebesiran (N=6)	Zilebesiran & Irbesartan (N=10)	Placebo (N=32)	All Zilebesiran (N=80)
AE, n (%)	24 (86)	42 (75)	4 (100)	3 (38)	6 (100)	7 (70)	28 (88)	58 (72)
Any serious AE, n (%)a	1 (4)	1 (2)	0	0	0	1 (10)	1 (3)	2 (2)
Any severe AE, n (%)b	1 (4)	1 (2)	0	0	0	0	1 (3)	1 (1)
Any AE leading to withdrawal, n (%)	0	0	0	0	0	0	0	0
Death, n (%)	0	0	0	0	0	0	0	0
AEs in ≥5% of patients, n (%)								
Headache	13 (46)	10 (18)	1 (25)	0	2 (33)	3 (30)	14 (44)	15 (19)
ISR	0	5 (9)	0	0	0	0	0	5 (6)
URTI	3 (11)	4 (7)	0	0	0	0	3 (9)	4 (5)
AEs of interest, n (%)c								
Hypotension	0	0	0	0	0	0	0	0
Hyperkalemia	0	0	0	0	0	0	0	0
Renal AE	0	0	0	0	0	0	0	0
Hepatic AE	0	1 (2)	1 (25)	0	0	0	1 (3)	1 (1)

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; ISR = injection-site reaction; MedDRA = Medical Dictionary for Regulatory Activities; URTI = upper respiratory tract infection.

[a]Serious AEs were defined as AEs that resulted in death, were life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators. All AEs (including serious AEs) were graded for severity. Serious AEs included optic ischemic neuropathy (grade 3 event, in a patient receiving placebo in Part A), prostate cancer (grade 3 event, in a patient receiving 200-mg zilebesiran in Part A) that was detected on biopsy during screening and resulted in surgery, and acute anemia (grade 1 event, in a patient receiving zilebesiran and irbesartan in Part E) due to a complication of esophagogastroduodenoscopy with biopsy performed during screening

[b]Severe events were AEs for which more than minimal, local, or noninvasive intervention was received; which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death.

[c]Hypotension AEs included hypotension, orthostatic hypotension, and diastolic hypotension. Hyperkalemia AEs included abnormal blood potassium, increased blood potassium, abnormal plasma potassium, increased plasma potassium, and hyperkalemia. Hepatic AEs included all events selected according to the MedDRA terms for drug-related hepatic disorders. One patient receiving placebo (in Part B) had a transient elevation in the alanine aminotransferase level greater than 3 times the upper limit of the normal range that was attributed to alcohol consumption; one patient receiving zilebesiran (25 mg, in Part A) had a transient elevation in the aspartate aminotransferase level of 2.2 times the upper limit of the normal range. Renal AEs included all the events selected according to the MedDRA terms for acute renal failure.

A summary of AEs in Part D is shown in **Table 4.** The majority of AEs were mild or moderate in severity, and headache was the only AE that occurred in ≥2 patients (37.5%) following treatment with zilebesiran. There was a treatment-emergent SAE of an abnormal FibroScan® result that occurred in a patient treated with zilebesiran. The event was classified as severe, serious, leading to study drug discontinuation, and was found to be unrelated to study drug by Investigators. A repeat scan after the data cut off suggested the patient had fatty liver. There was 1 event of increase in ALT (3.5x ULN) and 1 event of ISR occurring in the zilebesiran treatment arm, both of which were mild, transient, and found to be unrelated to study drug by Investigators.[2]

Table 4. Summary of AEs in Part D.[2]

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

Data cut off April 20, 2022.
Abbreviations: AE = adverse event; SAE = serious adverse event.

There were no deaths or unplanned hospitalizations that occurred, and no patients received interventions for hypotension, hyperkalemia, or worsening of kidney function across Parts A, B, and E. There were no episodes of hypotension requiring intervention in Part D. There were no clinically significant changes reported in serum levels of potassium, sodium, creatinine, or in eGFR. Transient, low-titer ADA were detected in 2% of patients (2/80) in Parts A, B, and E.[1,2]

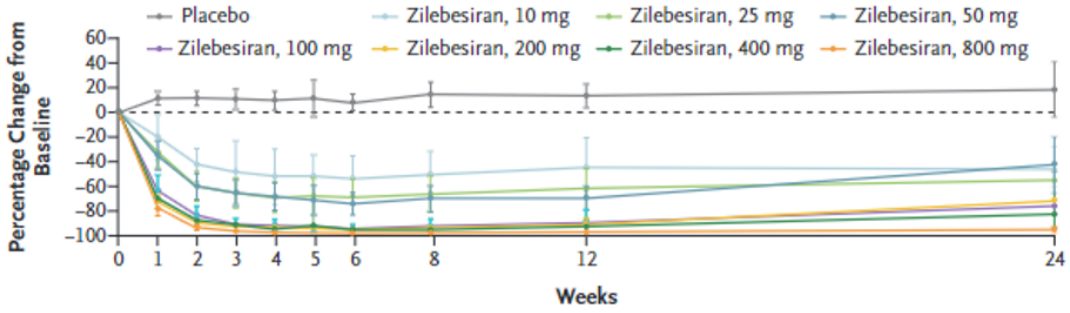
PHARMACODYNAMIC RESULTS

Change from Baseline in Mean Serum AGT Level

The change in serum AGT level was negatively correlated with the zilebesiran dose at week 8 in Part A (r=-0.56; 95% CI, -0.69 to -0.39). Doses of 100 mg of zilebesiran or more corresponded with mean decreases in serum AGT levels of more than 90%, sustained from week 3 through week 12 in Part A. Patients in Part A who received 800 mg of zilebesiran maintained decreases in serum AGT levels of more than 90% through week 24 (**Figure 1**). Similar decreases in serum AGT levels were seen at week 12 in Parts B and E (**Figure 2 and 3**, respectively). In Part E, the co-administration of irbesartan with zilebesiran did not result in an additional effect on AGT levels.[1]

In Part D, sequential doses of 800 mg of zilebesiran led to reductions in serum AGT levels (**Figure 4**). Following the first zilebesiran dose, mean serum AGT levels decreased by 96% at week 2 and 99% at week 4. Reductions were sustained through to week 24 following the second dose and were comparable to those in patients with a BMI ≤35 kg/m^2 following a single dose of zilebesiran.[2]

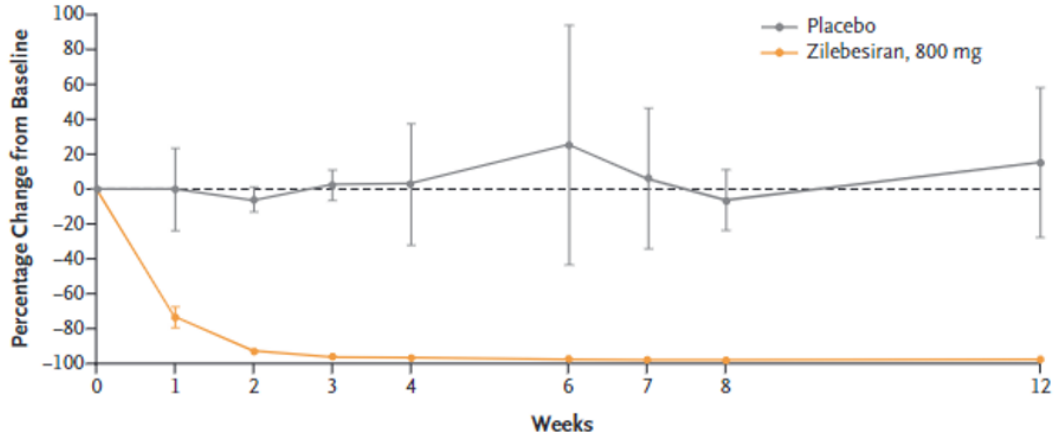
Figure 1. Change from Baseline in Mean Serum AGT Level Following a Single Dose of Zilebesiran in Part A.[1]



No. of Patients										
Placebo	28	28	28	28	27	17	26	27	28	12
Zilebesiran, 10 mg	8	8	8	8	8	8	8	8	8	5
Zilebesiran, 25 mg	8	8	8	8	8	8	8	8	8	8
Zilebesiran, 50 mg	8	8	8	8	8	8	8	7	7	7
Zilebesiran, 100 mg	8	7	8	8	8	8	8	8	7	7
Zilebesiran, 200 mg	8	8	8	7	6	2	3	7	8	8
Zilebesiran, 400 mg	8	8	8	8	8	0	8	8	8	8
Zilebesiran, 800 mg	8	8	8	8	8	0	8	8	8	8

From Desai et al.[1]

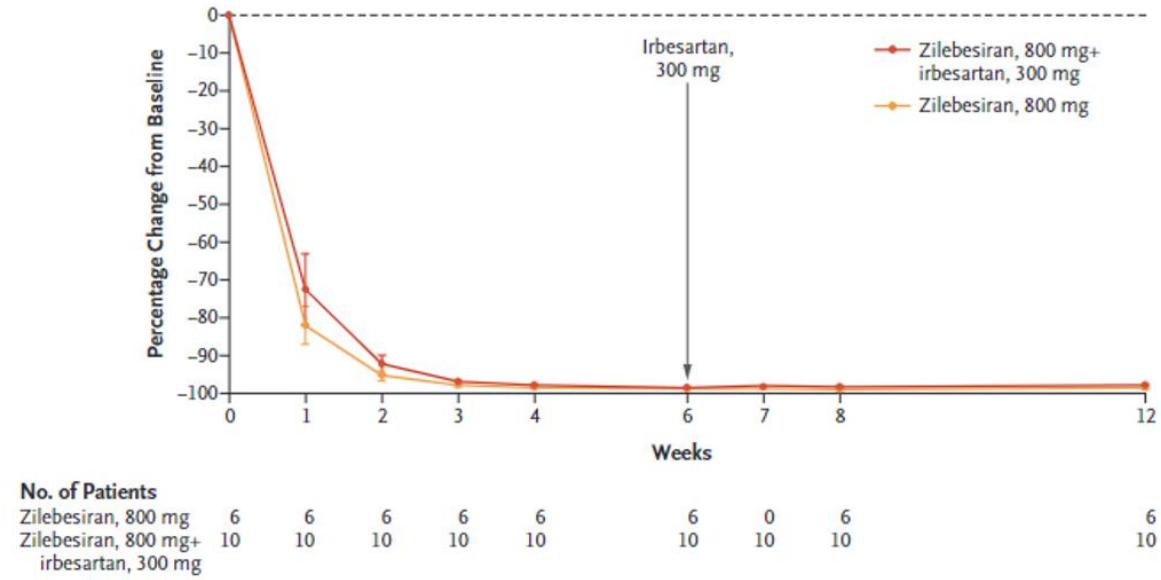
Figure 2. Change from Baseline in Mean Serum AGT Level Following a Single Dose of Zilebesiran in Part B.[1]



No. of Patients									
Placebo	4	3	4	4	4	4	4	4	4
Zilebesiran	8	8	8	8	8	8	8	8	8

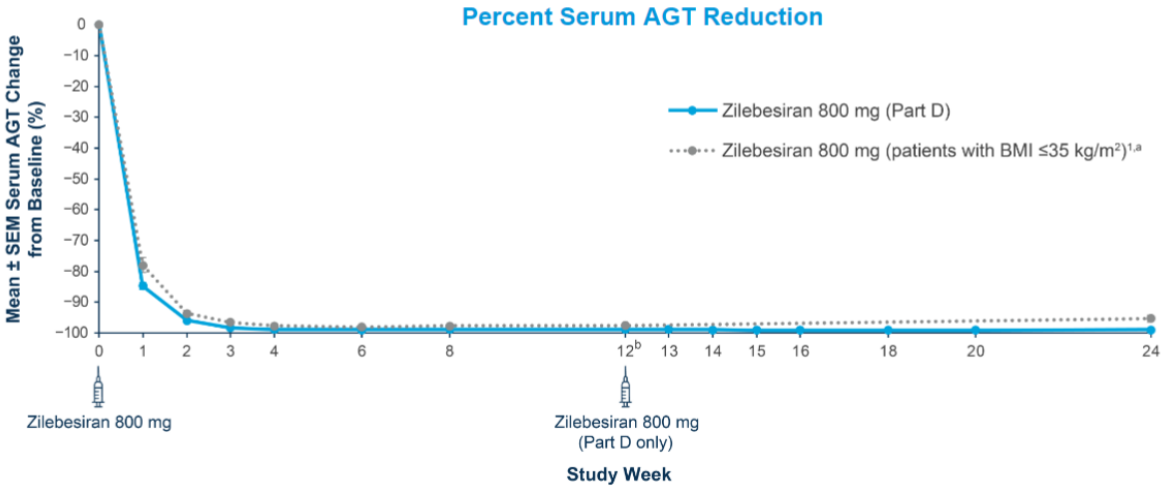
From Desai et al.[1]

Figure 3. Change from Baseline in Mean Serum AGT Level Following a Single Dose of Zilebesiran in Part E.[1]



From Desai et al.[1]

Figure 4. Change from Baseline in Mean Serum AGT Level Following Sequential Doses of Zilebesiran in Part D.[2]



Abbreviations: AGT = angiotensinogen; BMI = body-mass index; SD = standard deviation; SEM = standard error of the mean.
[a]Patients from Part A of the study; mean (SD) BMI of 28.6 kg/m2 (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.
From Taubel et al.[2]

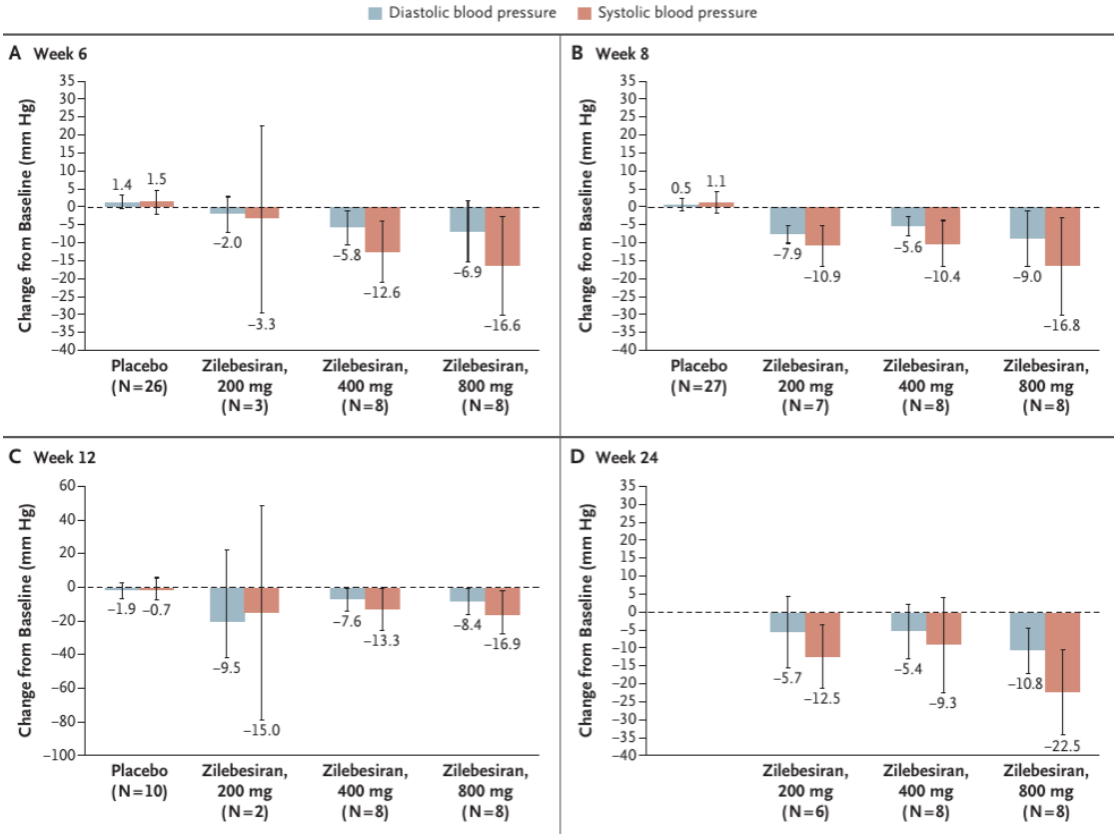
EXPLORATORY RESULTS

Change from Baseline in 24-h Ambulatory Blood Pressure (Parts A & D)

In Part A, there was a negative correlation between the zilebesiran dose and the change from baseline in the mean 24-hour ambulatory SBP (r=-0.41, 95% CI, -0.58 to -0.21). There was an observed decrease in the SBP which correlated with the decrease in serum AGT level (r=0.52; 95% CI, 0.42 to 0.61).

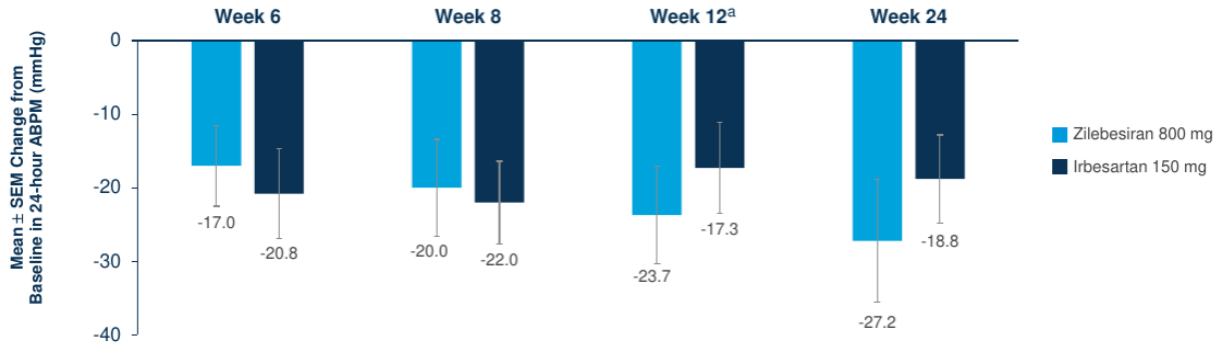
Decreases in SBP (>10 mmHg) and DBP (>5 mmHg) were seen after single doses of 200 mg or more of zilebesiran at week 8 (**Figure 5**).[1] In Part D, sequential doses of 800 mg of zilebesiran resulted in reductions in mean 24-hour ambulatory SBP, as shown in **Figure 6.**[2]

Figure 5. Decreases in SBP and DBP following a Single Dose of Zilebesiran in Part A at Weeks 6, 8, 12, and 24.[1]



Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure.
From Desai et al.[1]

Figure 6. Change from Baseline in 24-Hour Mean SBP in Part D at Weeks 6, 8, 12, and 24.[2]



Abbreviations: ABPM = ambulatory blood pressure monitoring; SBP = systolic blood pressure; SEM = standard error of the mean.
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.
[a]SBP measurements at Week 12 were taken the day before the second dose of zilebesiran.
From Taubel et al.[2]

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; ADA = anti-drug antibody; AE = adverse event; AGT = angiotensinogen; ALT = alanine aminotransferase; BMI = body-mass index; BP = blood pressure; CI = confidence interval; CV = cardiovascular; DBP = diastolic blood pressure; GFR = estimated glomerular filtration rate; ISR = injection-site reaction; mRNA = messenger RNA; PD = pharmacodynamic; PK = pharmacokinetic; PO = oral; RAAS = renin-angiotensin-aldosterone system; RNAi = RNA interference; SAE = serious adverse event; SBP = systolic blood pressure; SC = subcutaneous; SD = standard deviation; SEM = standard error of the mean; ULN = upper limit of normal; URTI = upper respiratory tract infection.

Updated 9 July 2025

REFERENCES

1. Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N Engl J Med*. 2023;389(3):228-238. doi:10.1056/NEJMoa2208391
2. Taubel J, Desai AS, Lasko M, et al. Safety and tolerability of zilebesiran, an RNA interference therapeutic targeting hepatic angiotensinogen synthesis, in obese patients with hypertension. Presented at: American Heart Association (AHA) Hypertension Scientific Sessions; September 7-10, 2023; Boston, MA, USA.