Durable Reductions in Circulating Angiotensinogen and Blood Pressure 6 Months after Single Doses of ALN-AGT, an RNA Interference Therapeutic Targeting Hepatic Angiotensinogen Synthesis, in Hypertensive Patients

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Zilebesiran (ALN-AGT) is under investigation for the treatment of hypertension.

Disclosures

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David Webb
AbbVie: Consulting fees
AstraZeneca: Trial steering committee
Idorsia: Investigator
Janssen: Consulting fees

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Background and Rationale

Hypertension

- Hypertension is a leading cause of mortality and morbidity worldwide[1-5]
- Despite effective antihypertensives, hypertension is uncontrolled in ~50% of patients and >50% of patients are non- or suboptimally adherent[1-5]
- The RAAS has a demonstrated role in BP regulation[6,7]
  - AGT is the most upstream precursor in the RAAS[7]

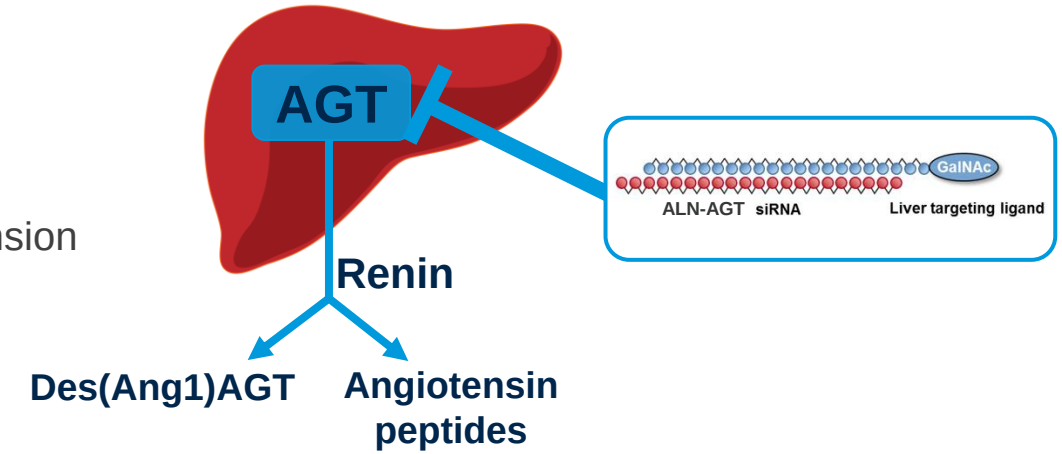
Zilebesiran

- Zilebesiran (ALN-AGT), a SC administered RNAi therapeutic targeting hepatic AGT synthesis is under investigation for the treatment of hypertension
- Potential mechanistic advantages of RNAi:
  - Liver-specific AGT silencing
  - Prolonged duration of action
    - Consistent and durable BP response
    - Infrequent dose administration
    - Potential for improved adherence

Objective

- To assess the safety and efficacy of zilebesiran 6 months after single-dose administration in a Phase 1 study

Liver-Specific AGT Knockdown



AGT, angiotensinogen; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system; RNAi, ribonucleic acid interference; SC, subcutaneous.

1. McClellan M et al. *Circulation* 2019;139:e44–e54; 2. Zhou B et al. *Nat Rev Cardiol* 2021;18:785–802; 3. Burnier M & Egan BM. *Circ Res* 2019;124:1124–1140; 4. Kotseva K et al. *Eur J Prev Cardiol* 2016;23:636–648; 5. Yoon SS et al. *NCHS Data Brief* 2015;1–8; 6. Te Riet L et al. *Circ Res* 2015;116:960–975; 7. Kumar R et al. In: Mann D, ed. *Heart Failure: A Companion to Braunwald's Heart Disease,* 2nd Edition. Saunders Press; 2010:134–151.

Multicenter, Randomized, Double-Blind Placebo-Controlled, Single Ascending Dose Study[a]

- Change from baseline BP was measured by 24-hour ABPM at Week 8, Week 12, and Week 24
- After Week 8, if a patient developed clinically significant elevated BP, add-on treatment could be initiated[b]
- Interim results for the secondary endpoints as of May 28, 2021 are reported

Patient Population
(N=12 per dose cohort; 2:1 zilebesiran: placebo)

- Adults 18 to 65 years of age
- SBP >130 and ≤165 mmHg without antihypertensive medications
- 24-hour ABPM SBP ≥130 mmHg
- BMI ≥18 and ≤35 kg/m^2
- Secondary hypertension excluded
- Treatment naïve or had prior antihypertensives washed out for ≥2 weeks before screening

2:1 RANDOMIZATION

- Zilebesiran 10 mg SC × 1
- Zilebesiran 25 mg SC × 1
- Zilebesiran 50 mg SC × 1
- Zilebesiran 100 mg SC × 1
- Zilebesiran 200 mg SC × 1
- Zilebesiran 400 mg SC × 1
- Zilebesiran 800 mg SC × 1

OR

- Placebo SC × 1

Primary Endpoint

- Safety and tolerability (data presented previously[1])

Key Secondary Endpoint

- Change from baseline in serum AGT

Exploratory Endpoint

- Change from baseline in SBP/DBP by 24-hour ABPM

[a]ClinicalTrials.gov identifier: NCT03934307. [b]For symptomatic or persistently elevated BP, at the discretion of the Investigator and in line with current hypertension management guidelines.
ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SC, subcutaneous

1. Desai et al. Oral presentation at European Society of Hypertension Congress 2021; Virtual.

Baseline Demographics and Characteristics

- A total of 84 patients with hypertension were enrolled in ascending single dose cohorts of zilebesiran up to 800 mg

Characteristic		Placebo (N=28)	Zilebesiran Dose Cohort							All Zilebesiran (N=56)
			10 mg (n=8)	20 mg (n=8)	50 mg (n=8)	100 mg (n=8)	200 mg (n=8)	400 mg (n=8)	800 mg (n=8)	
Age, years; median (range)		52 (36–64)	53 (37–60)	56 (47–63)	41 (35–64)	56 (35–65)	56 (43–64)	58 (44–64)	61 (45–62)	55 (35–65)
Gender, n	Male	16	7	2	7	3	5	7	4	35
	Female	12	1	6	1	5	3	1	4	21
Race, n	White	21	6	4	3	4	6	6	6	35
	Black	6	1	4	4	2	2	1	2	16
	Asian	0	1	0	0	2	0	0	0	3
	Other	1	0	0	1	0	0	1	0	2
Blood Pressure (24-hour ABPM, mmHg)	SBP median (range)	142 (126–153)	139 (130–147)	140 (132–157)	135 (113–144)	137 (131–152)	139 (129–154)	138 (132–160)	142 (131–167)	137 (113–167)
	DBP median (range)	88 (72–103)	84 (76–93)	91 (75–103)	83 (74–91)	86 (80–90)	83 (75–95)	90 (76–99)	88 (75–102)	85 (74–103)

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure

Safety and Tolerability

Evaluated Per Protocol During the Double-Blind Phase[a] (12-Week Timepoint)

Number of Patients with at Least One Event, n	Placebo (N=28)	Zilebesiran Dose Cohort						All ALN-AGT (N=56)
		10 mg (n=8)	25 mg (n=8)	50 mg (n=8)	100 mg (n=8)	200 mg (n=8)	400 mg (n=8)	800 mg (n=8)	
Adverse Event	24	5	7	6	7	7	4	6	42
Serious Adverse Event	1	0	0	0	0	1	0	0	1
Severe Adverse Event	1	0	0	0	0	1	0	0	1

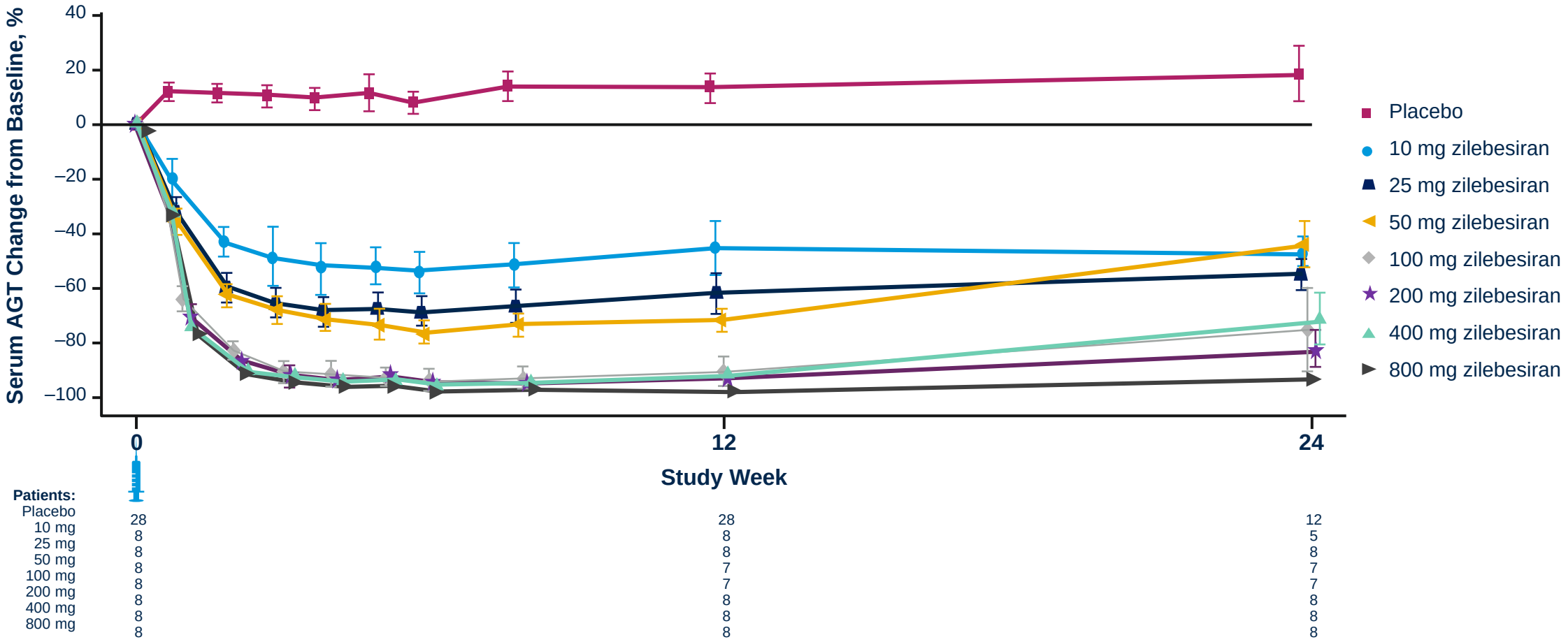
- Most AEs were mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal were reported
- No treatment-related serious AEs (SAEs) were reported
  - A severe SAE of prostate cancer was reported in one patient who received 200 mg zilebesiran, based on a biopsy that was performed during the screening period and reported as positive after dosing
  - A severe SAE of optic ischemic neuropathy was reported in one patient who received placebo
  - No additional SAEs were observed through Week 24
- No patient required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium were reported
- Five patients treated with zilebesiran had injection site reactions, all mild and transient

[a]Patients were unblinded after Week 12. Patients treated with zilebesiran entered a follow-up period and patients treated with placebo were not required to complete a safety follow-up period.

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event

Durable Dose-Dependent Lowering of AGT

- A reduction of ≥90% in serum AGT from baseline was observed with single doses of zilebesiran ≥100 mg from Week 3 and sustained to Week 12
- All patients who received a single dose of zilebesiran 800 mg maintained reduction of >90% in serum AGT to Week 24

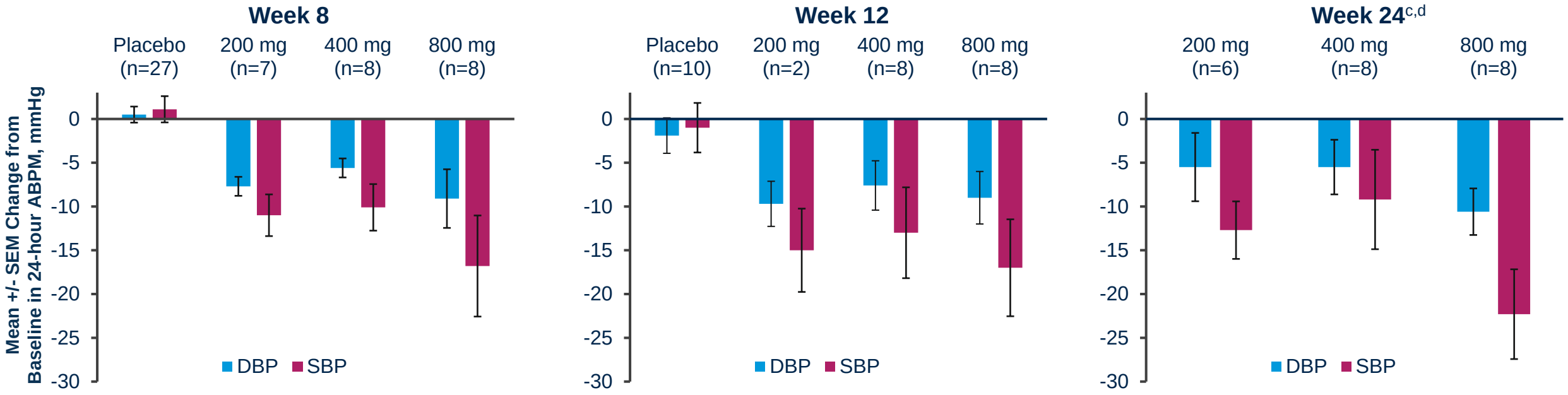


AGT, angiotensinogen

Durable Antihypertensive Effect of Single Dose Zilebesiran

- A mean 24-hour SBP reduction of >10 mmHg was achieved at Week 8 across dose groups ≥200 mg
  - Clinically meaningful reductions in BP were maintained through Week 24
- After a single dose of zilebesiran 800 mg, a mean 24-hour SBP reduction of >20 mmHg was observed at Week 24
  - Of the 8 patients in this group, 6 achieved a mean 24-hour SBP reduction of >20 mmHg at Week 24 without add-on antihypertensives
- Serum AGT reduction correlated with 24-hour SBP reduction across multiple doses[a]

ABPM Mean Change From Baseline[b]

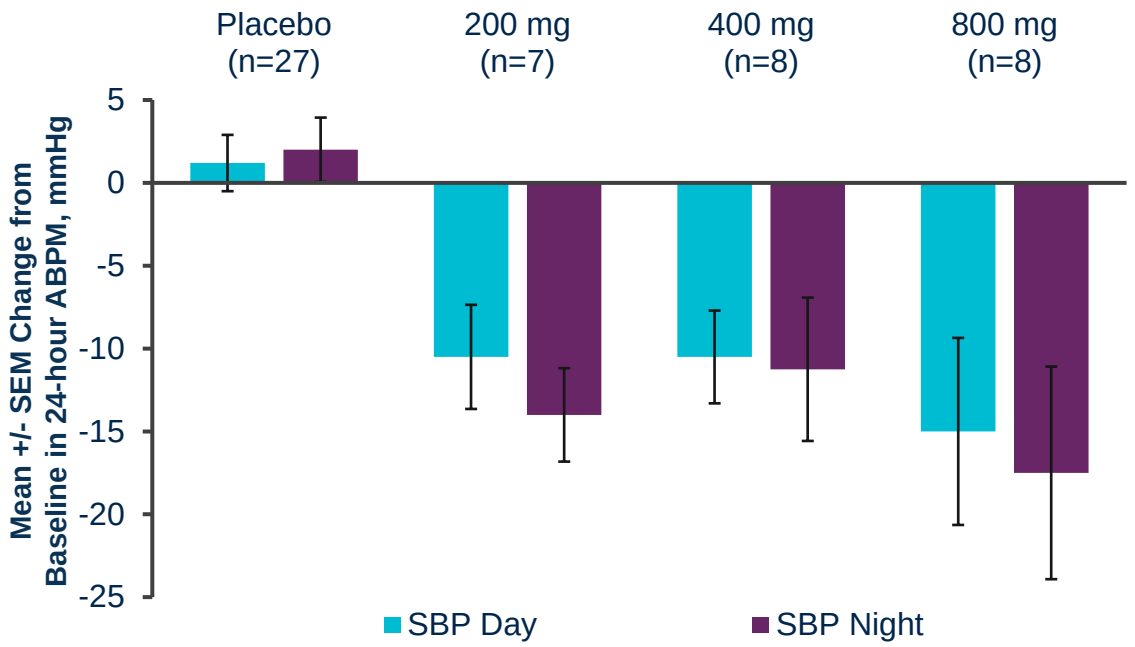


[a]Based on modelling using all available time-matched serum AGT and 24h SBP data from Phase 1 SAD cohort. [b]Median baseline SBP/DBP: Placebo – 142/88 mmHg; 200 mg – 139/83 mmHg; 400 mg – 138/90 mmHg; 800 mg – 142/88 mmHg. [c]After Week 12, patients on placebo were not required to be followed. [d]2 patients in the 200 mg dose group, 1 patient in 400 mg, and 2 patients in 800 mg received add-on antihypertensive therapy.
ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean.

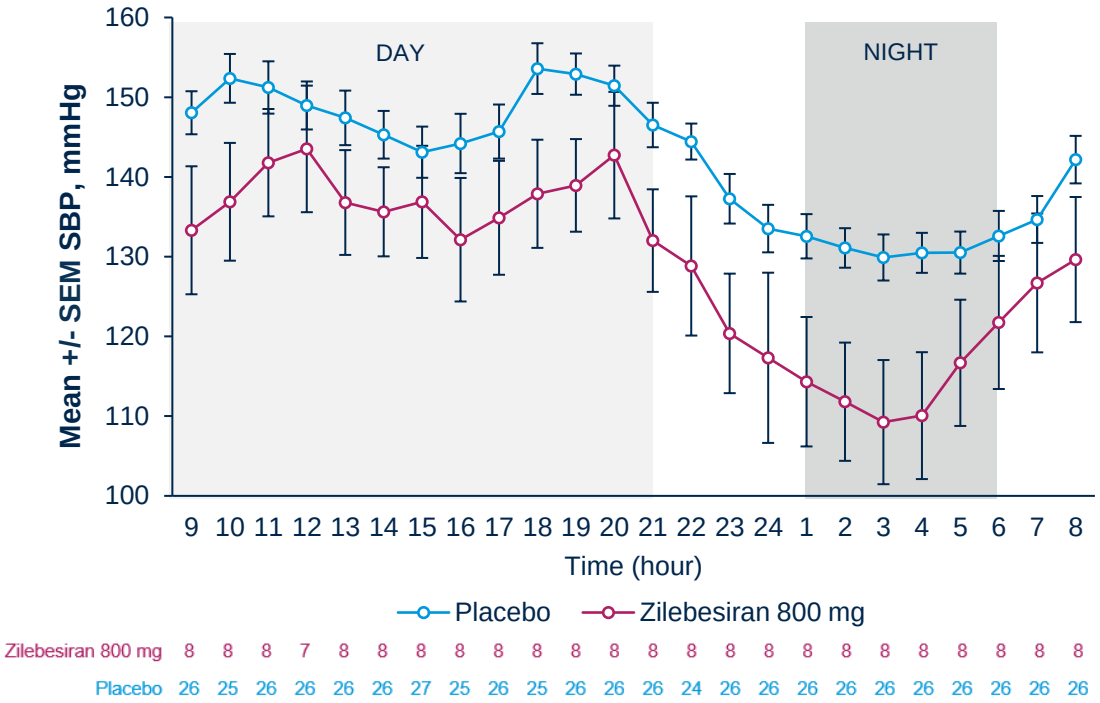
Consistent BP Reductions Over 24 Hours

- Marked reductions in both daytime and nighttime SBP were demonstrated with zilebesiran doses ≥200 mg at Week 8[a]
  - These reductions in daytime and nighttime SBP were sustained to later timepoints (Weeks 12 and 24; data not shown)
  - Similar improvements during daytime and nighttime were also seen for DBP (data not shown)

Change From Baseline in Daytime/Nighttime ABPM at Week 8[b,c]



24-Hour SBP at Week 8



[a]All patients at Week 8 were receiving zilebesiran only (no rescue antihypertensives). [b]Hourly adjusted mean; daytime [9 am to 9 pm], nighttime [1 am to 6 am]. [c]Median baseline SBP/DBP: Placebo – 142/88 mmHg; 200 mg – 139/83 mmHg; 400 mg – 138/90 mmHg; 800 mg – 142/88 mmHg

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean.

Summary and Conclusions

- A single SC dose of zilebesiran was well tolerated in patients with mild-to-moderate hypertension, supporting its continued development in patients with hypertension
- Sustained reduction in serum AGT >90% was observed through Week 24 after a single SC dose of zilebesiran 800 mg
- At Week 24, a clinically meaningful BP reduction was maintained across all dose groups ≥200 mg, with a mean 24-hour SBP reduction of >20 mmHg after a single dose of zilebesiran 800 mg
- Zilebesiran produced consistent and sustained reduction in BP throughout both daytime and nighttime
- These data support further evaluation of both quarterly and biannual dose administration of zilebesiran in hypertension

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

AGT, angiotensinogen; BP, blood pressure; SBP, systolic blood pressure; SC, subcutaneous.