Dose-Related and Prolonged Reductions in Blood Pressure with a RNAi Therapeutic Targeting Angiotensinogen in Hypertensive Patients: Interim Results from a Phase 1 Study with Zilebesiran (ALN-AGT01)

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Investigators and Contributors

Zilebesiran Phase 1 Study

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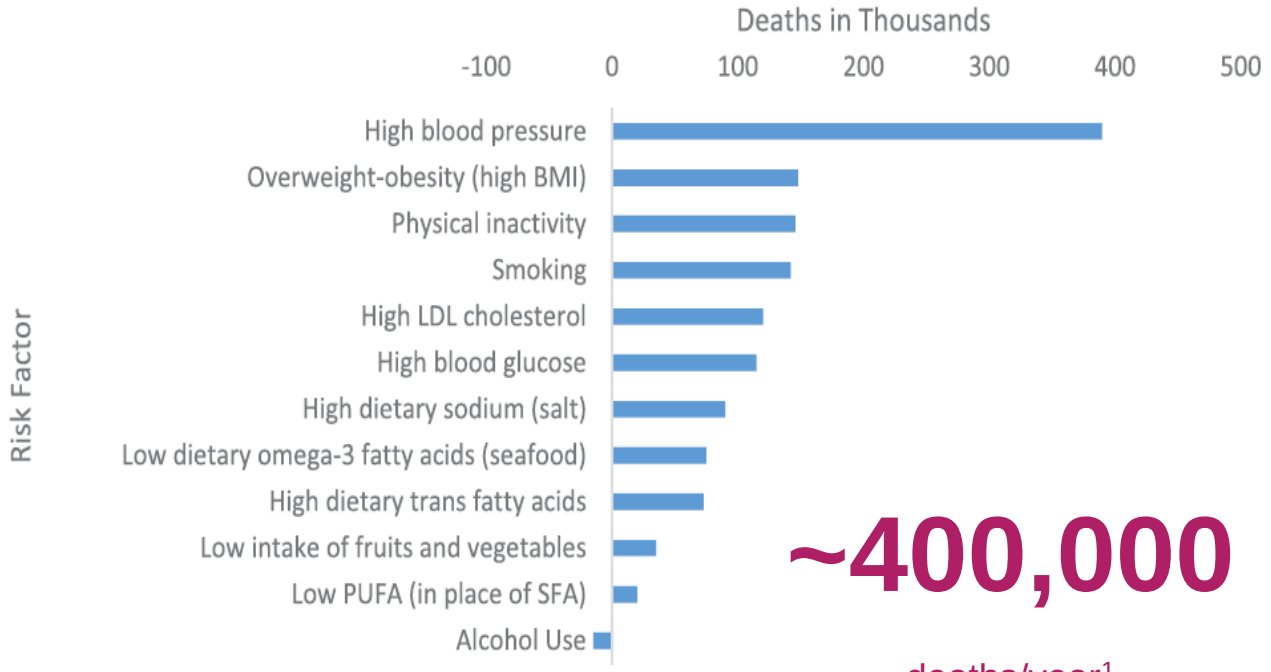
Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the ALN-AGT Phase 1 study

Background

Hypertension remains the leading cause of death and disability-adjusted life-years worldwide[1–4]…



~400,000

deaths/year[1]

…but treatment of hypertension remains suboptimal despite availability of effective antihypertensives[1–4]

Approx. half of all patients with hypertension are not controlled to guideline-recommended targets

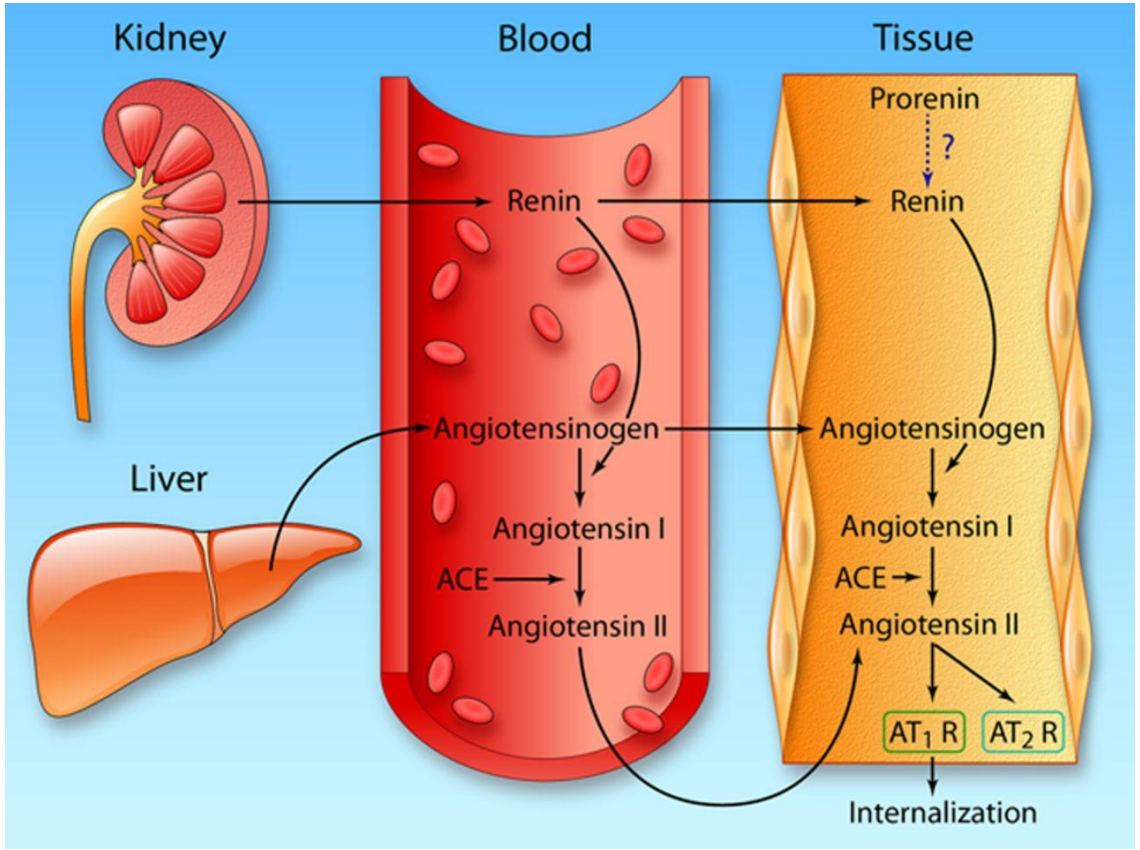
>50% of patients are nonadherent or suboptimally adherent to antihypertensive treatment

Figure permission pending

BMI, body mass index; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid

1. McClellan et al., *Circulation* 2019; 2. Chang TE et al., *Hypertension*, 2019; 3. Carey RM et al., *Hypertension*, 2018; 4. Elliott WJ, *J Clin Hypertens*, 2016

AGT is the First Substrate in the RAAS Cascade



The Renin-Angiotensin-Aldosterone System (RAAS) cascade has a demonstrated role in blood pressure regulation[1,2]

- Traditional RAAS-targeted anti-hypertensive pharmacotherapy targets include…
  - Renin inhibition
  - Inhibition of angiotensin converting enzyme (ACE)
  - Inhibition of angiotensin II (ANG II) receptor binding

Angiotensinogen (AGT) is the most upstream precursor of the RAAS cascade, and is predominantly produced in the liver[2]

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1. te Reit, L et al. *Circ Res*. 2015. 116(6): 960-975; 2. Kumar, R. et al. *Heart Failure: A Companion to Braunwald's Heart Disease, 2nd* Edition, by Douglas Mann, Saunders Press 2011, pp. 134-151; 3. Uijl E. et al. *Hypertension*. 2019. 73:1249-1257.

Angiotensinogen (AGT) is a Genetically Validated Target

AGT is First Gene Linked to Primary Hypertension[1]; Multiple Lines of Evidence Support Causal Association[2,3]

Three Independent Lines of Evidence Replicated in Independent Samples from Salt Lake City and Paris

- Linkage of AGT locus with primary hypertension in hypertensive sibling pairs
- Association of specific AGT variants with primary hypertension in case-control studies
- Association of same variants with elevated plasma AGT levels

Role of AGT in Genetics of Blood Pressure Regulation Confirmed in Large GWAS Study of 342,415 Individuals

- AGT locus highly significantly associated with:
  - Systolic BP (P value = 9.65×10^{-13}) and
  - Diastolic BP (P value = 9.53×10^{-15})

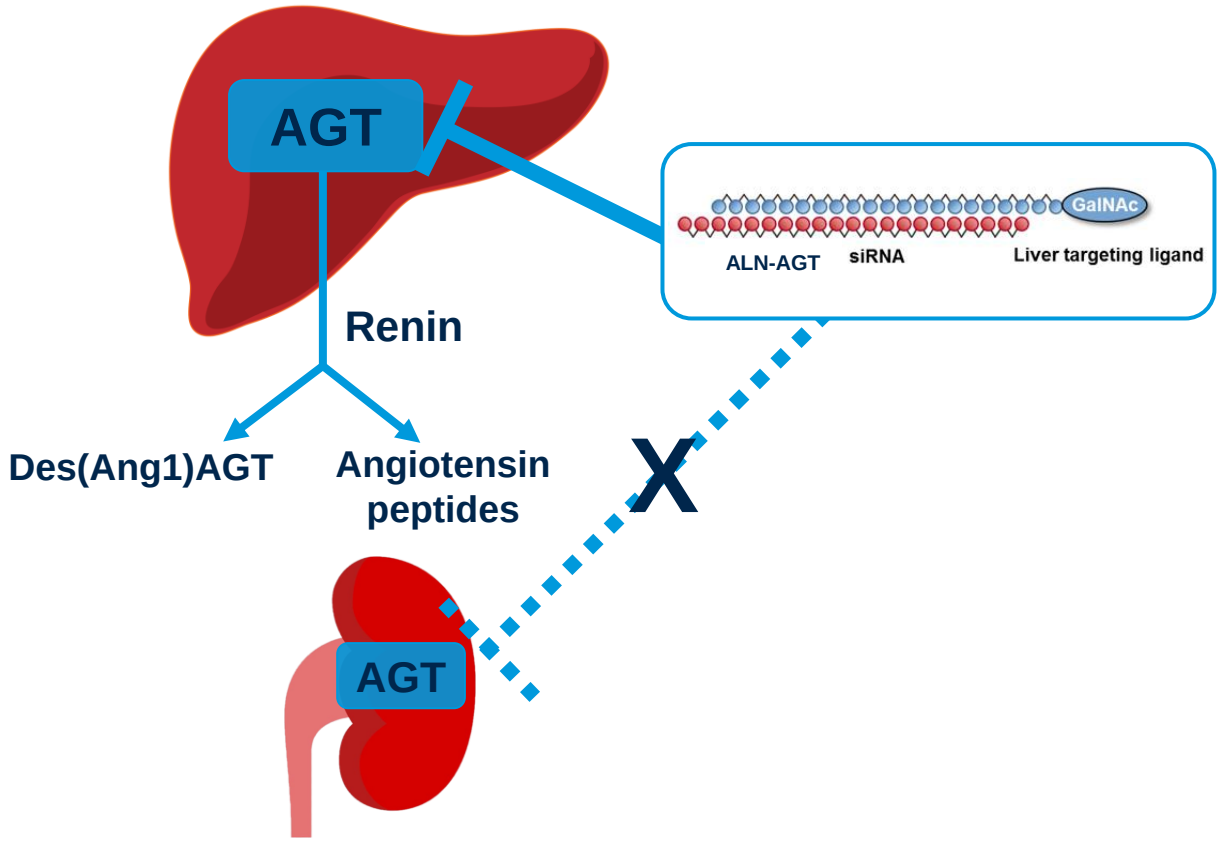
AGT, angiotensinogen; BP, blood pressure; GWAS, genome-wide association study

1. Jeunemaitre X et al. Cell, 1992; 2. Lifton RP , Science, 1996; 3. Ehret GB et al. Nature Genetics, 2016

Zilebesiran Therapeutic Hypothesis

An Investigational RNAi Therapeutic

Liver-specific AGT Knockdown

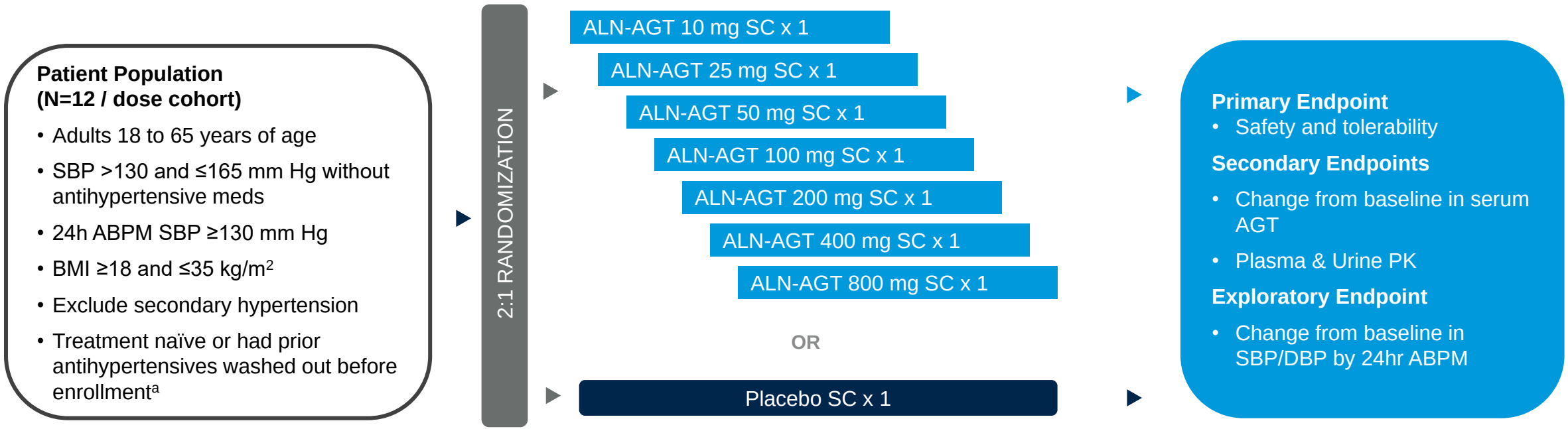


- **Liver-specific silencing of AGT**
- **Prolonged duration of action**
  - Consistent and durable BP response
  - Potential for infrequent dose administration

AGT, angiotensinogen; BP, blood pressure; GalNAc, N-acetylgalactosamine; siRNA, small interfering ribonucleic acid

Zilebesiran First-in-Human Single Ascending Dose Study

- A total of 84 patients with hypertension completed treatment as of 25-February-2021
- Patients received either placebo (n=4 per cohort) or ALN-AGT (n=8 per cohort)
- Study conducted in outpatient setting with usual activity and dietary sodium intake



[a]Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to screening

ClinicalTrials.gov Identifier: NCT03934307

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; DBP, diastolic blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous

Baseline Demographics and Characteristics

Characteristic		Placebo (N=28)	ALN-AGT 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)	
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	**Male**	16	7	2	7	3	5	7	4	35
	Female	12	1	6	1	5	3	1	4	21
Race	**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	**24h ABPM 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)
	24h ABPM 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

Primary Endpoint: Safety & Tolerability

ALN-AGT Was Generally Well-Tolerated Supporting Continued Development

At Least One Event, n	Placebo (N=28)	ALN-AGT 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	2	0	0	0	0	1	0	0	1

- Most AEs mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal
- No treatment-related Serious AEs (SAEs)
  - Severe and serious AE of prostate cancer reported in 1 patient who received 200 mg ALN-AGT, based upon a biopsy that was performed in the screening period and reported as positive after dosing
- 5 patients who received zilebesiran had injection site reactions, all mild and transient
- No patient has required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium

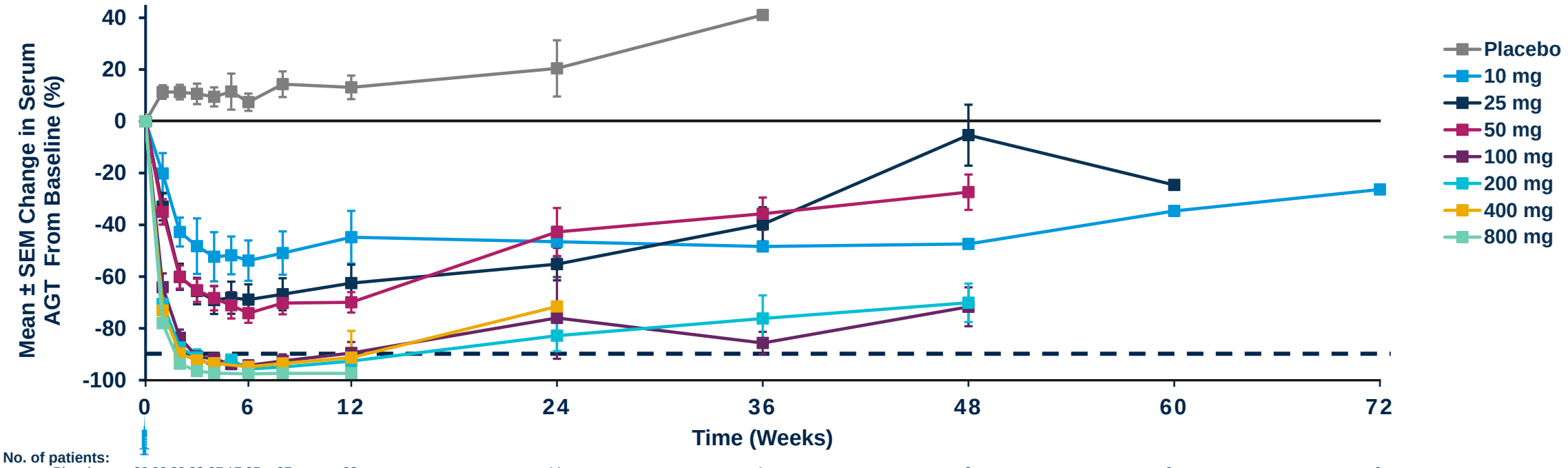
Safety data presented as of 25 February 2021

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

Secondary Endpoint: Dose-Dependent AGT Lowering

Durable Reduction of Serum AGT >90% Sustained for 12 weeks After Single Doses of ALN-AGT ≥ 100 mg

- Serum AGT reduced 96-98% at Week 12 in all patients given single dose of 800 mg



No. of patients:

Placebo	28	28	28	28	27	17	25	27	28	11	1	0	0	0
10 mg	8	8	8	8	8	8	8	8	8	5	2	1	1	1
25 mg	8	8	8	8	8	8	8	8	8	8	6	6	1	0
50 mg	8	8	8	8	8	8	8	7	7	7	4	2	0	0
100 mg	8	7	8	8	8	8	8	8	7	7	6	5	0	0
200 mg	8	8	8	7	6	2	3	7	8	8	4	5	0	0
400 mg	8	8	8	8	8	0	8	8	8	8	0	0	0	0
800 mg	8	8	8	7	8	0	8	8	8	0	0	0	0	0

Data presented as of 25 February 2021

AGT, angiotensinogen; SEM, standard error of the mean

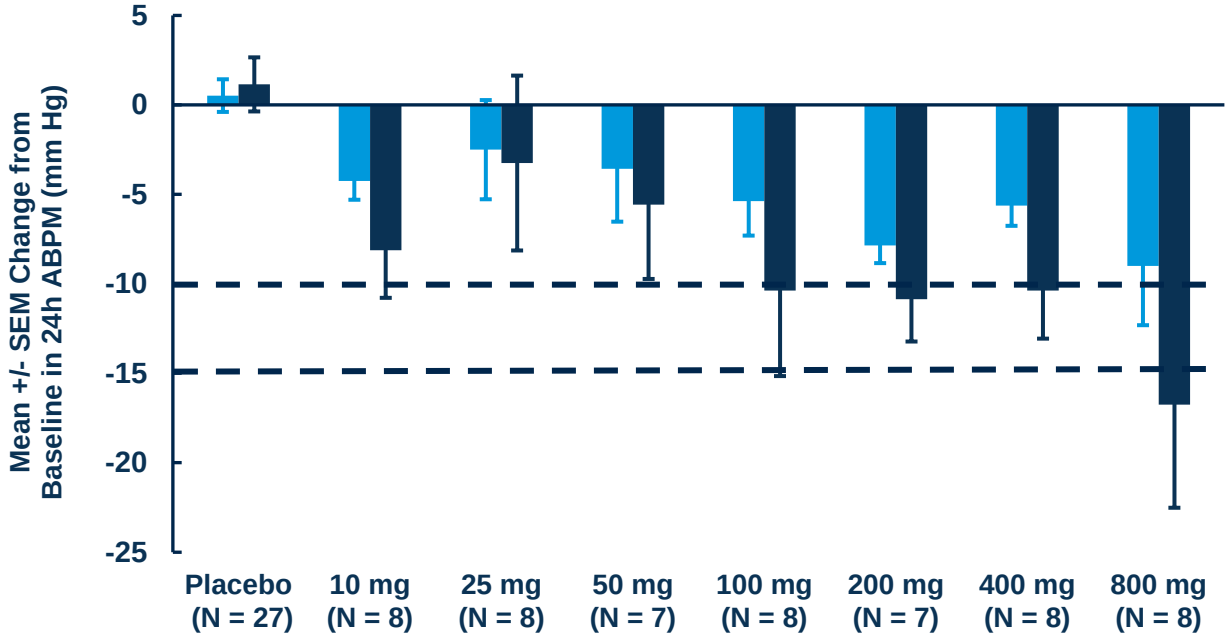
Exploratory Endpoint: Dose-Dependent Reductions in BP

24h SBP Reduction >10 mm Hg at 8 Weeks After Single Doses of ALN-AGT ≥100 mg

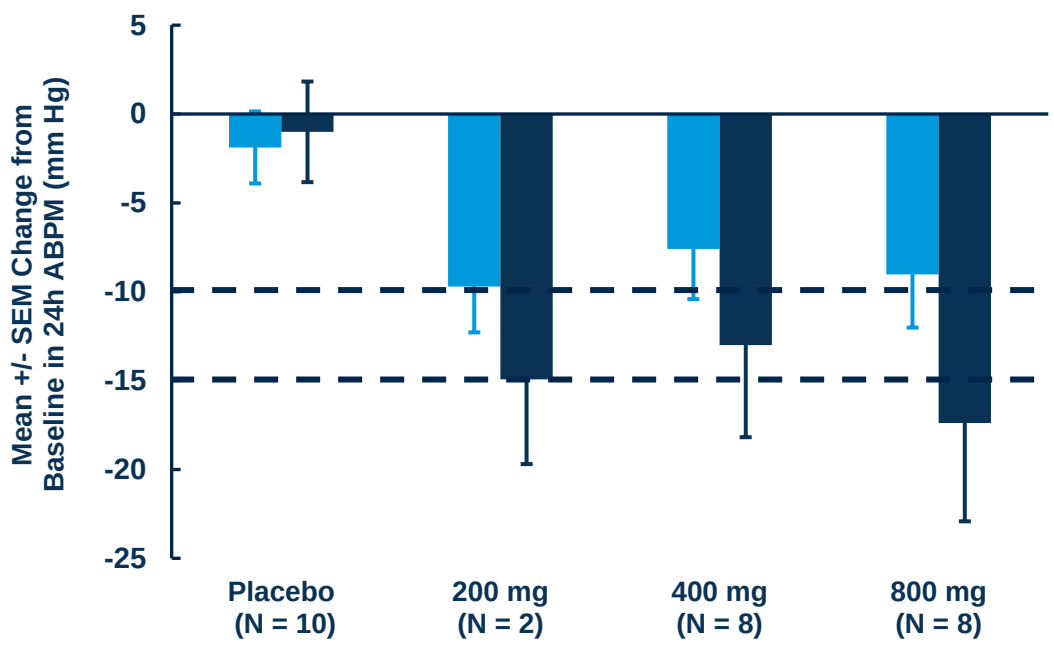
24h SBP Reduction >15 mm Hg at 8 Weeks After Single Doses of ALN-AGT 800 mg

- Mean 24h blood pressure reduction of 17 mm Hg / 9 mm Hg at Week 12 in patients given single dose of 800 mg

ABPM Change from Baseline at Week 8



ABPM Change from Baseline at Week 12*



Diastolic Blood Pressure Systolic Blood Pressure

Data presented as of 25 February 2021

*Protocol amended to collect Week 12 ABPM data during dosing of the 200 mg cohort

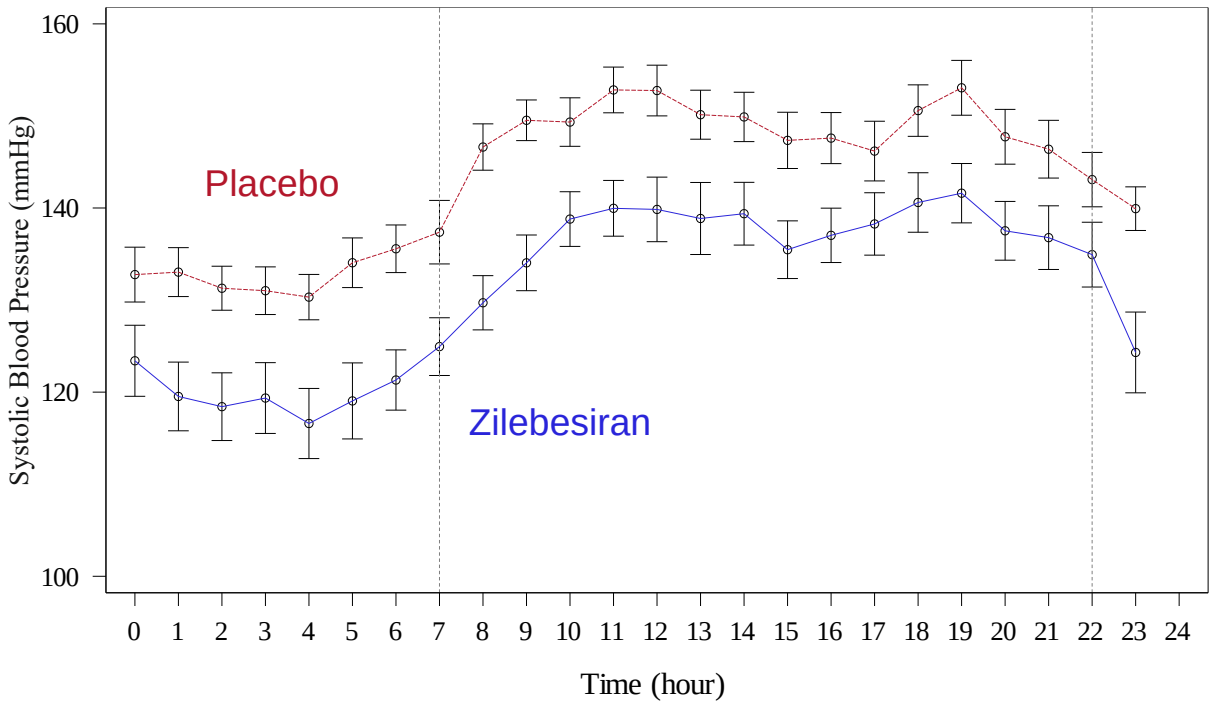
ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean

Exploratory Endpoint: 24-Hour Blood Pressure Profile

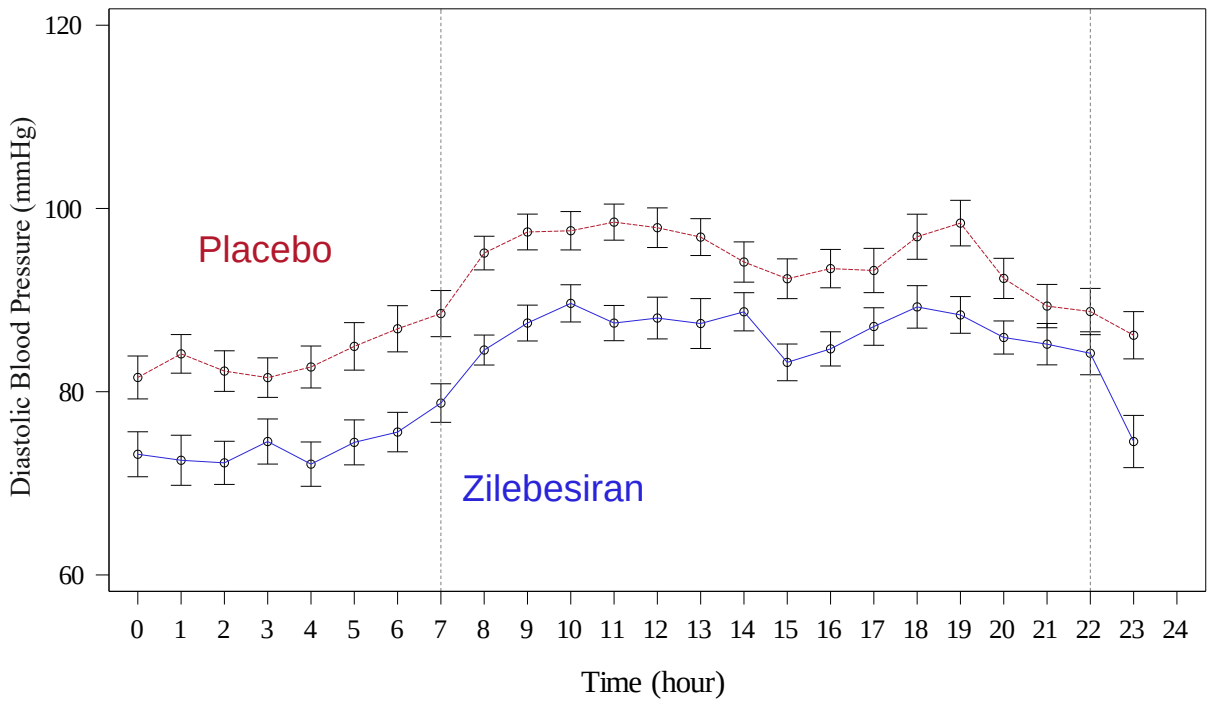
Blood Pressure Profiles 6 Weeks After Single Dose of Zilebesiran (800mg) or Placebo

- BP Reduction at All Timepoints During the 24-Hour Period

Systolic BP



Diastolic BP



All Week 6 ABPM data as of 28-May-2021 pooled from patients treated with placebo (N = 28) vs. zilebesiran 800 mg (N = 32) in Phase 1

Ongoing Additional Phase 1 Study Cohorts

- Cohort designed to assess zilebesiran tolerability during extracellular fluid volume reduction caused by salt depletion
- Irbesartan-coadministration cohort designed to assess combinability with conventional RAAS blockade
- Multidose cohort designed to assess potential effects of zilebesiran in obese patients

Phase 2 Clinical Development Plan

KARDIA$_1$

Monotherapy Phase 2 Study (N ~375)

- IND filing expected year-end 2022
- Evaluate efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension
- Exploring both quarterly and biannual dosing regimens
- Study initiated June 2021

KARDIA$_2$

Add-On Phase 2 Study

- Phase 2 combination therapy study of zilebesiran
- Targeting study initiation in late 2021

Zilebesiran KARDIA-1 Phase 2 Study

Randomized, Double-blind, Placebo-Controlled Study in Patients with Mild-to-Moderate Hypertension

N ~ 375
Patient Population

Key Inclusion Criteria:
- 18 - 75 years of age
- Daytime SBP ≥135 & ≤160 mm Hg
- Treatment naive or prior antihypertensives washed out before enrollment

Key Exclusion Criteria:
- Secondary HTN
- eGFR <30 ml/min/1.73m^2

ClinicalTrials.gov Identifier: NCT04936035

4-Week Washout

1:1:1:1:1 RANDOMIZATION

- **Zilebesiran** 150 mg SC q6M
- **Zilebesiran** 300 mg SC q6M
- **Zilebesiran** 300 mg SC q3M
- **Zilebesiran** 600 mg SC q6M
- **Placebo*** SC q3M

Primary Endpoint
- Change in SBP from baseline to Month 3 assessed by ABPM

Secondary Endpoints Include (through Month 6)
- Change in SBP and DBP by ABPM
- Time-adjusted change in SBP and DBP by office BP

Exploratory Endpoints Include (through Month 12)
- Change in 24h average, daytime average, and night-time average SBP and DBP
- Time-adjusted change in SBP and DBP assessed by office BP, home BP monitoring, and ABPM

Study Initiated
June 2021

* Placebo randomized across four zilebesiran treatment arms after 6 months on study

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; q3M: every 3 months (quarterly); q6M: every 6 months (semiannual); ABPM: ambulatory blood pressure measurement

Conclusion

- Single subcutaneous doses of zilebesiran were generally well tolerated in patients with mild to moderate hypertension in an interim analysis of an ongoing Phase 1 study, supporting continued development
- Patients receiving zilebesiran had dose-dependent and durable reduction of serum AGT
- Serum AGT reductions >90% sustained to 3 months after single doses of zilebesiran ≥100 mg
- Patients receiving zilebesiran had >10 mm Hg reduction in 24h SBP at 8 weeks after single doses of 100 mg or higher and >15 mm Hg reduction in 24h SBP after single doses of 800 mg
- Phase 1 data indicate potential for quarterly or biannual dosing; both regimens to be evaluated in Phase 2 studies
- KARDIA-1 and KARDIA-2 Phase 2 studies currently being initiated