Dose-Related Reductions in Blood Pressure with a RNA Interference (RNAi) Therapeutic Targeting Angiotensinogen in Hypertensive Patients: Interim Results from a First-In-Human Phase 1 Study of ALN-AGT01

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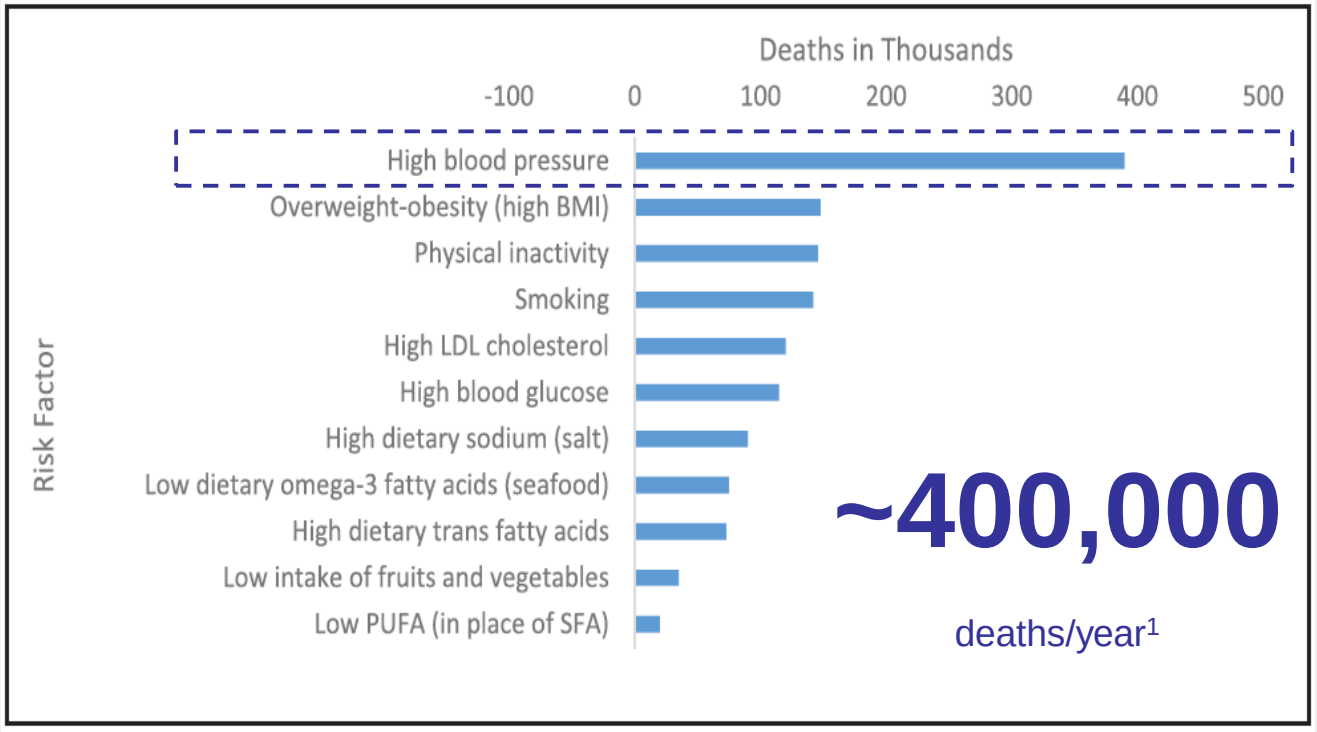
BACKGROUND

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



Adapted from McClellan et al., 2019[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

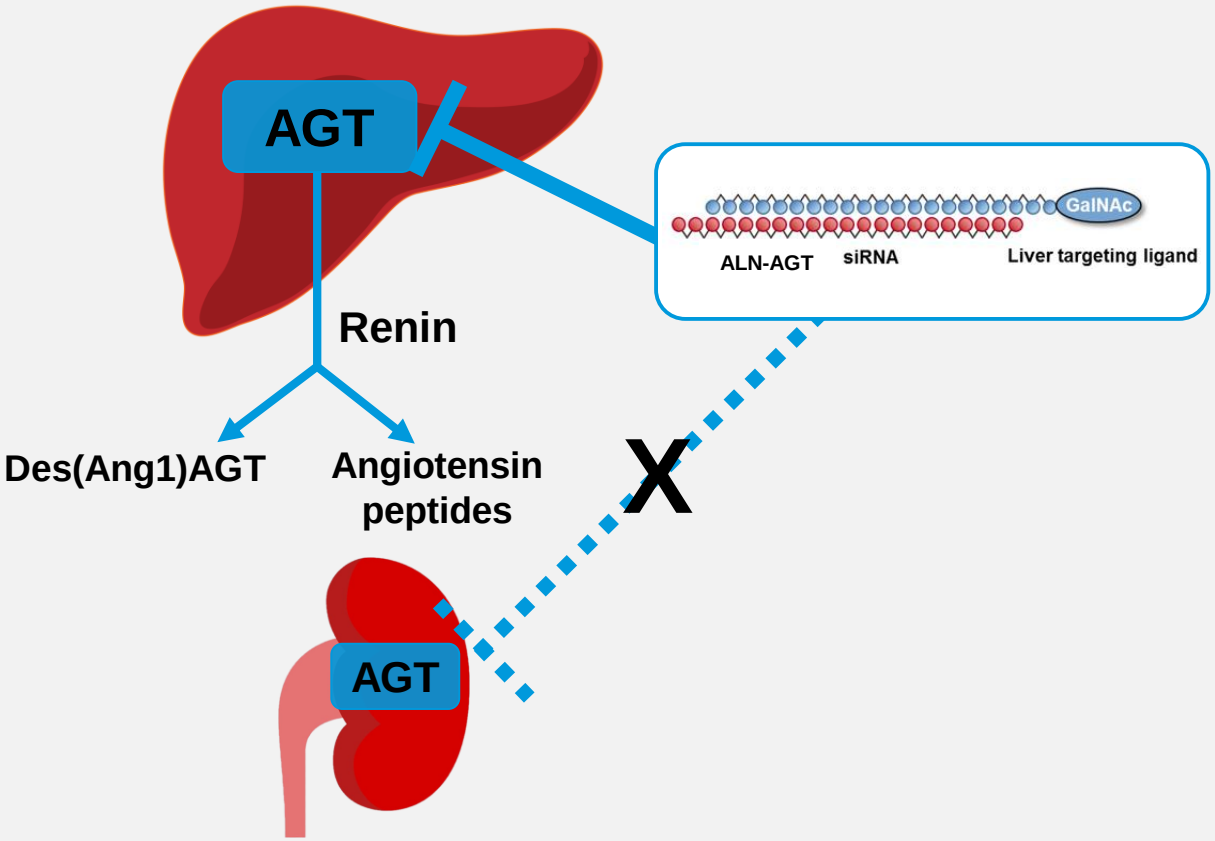
>50% of patients are nonadherent or suboptimally adherent to antihypertensive treatment

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

ALN-AGT01 Therapeutic Hypothesis

Liver-specific AGT Knockdown



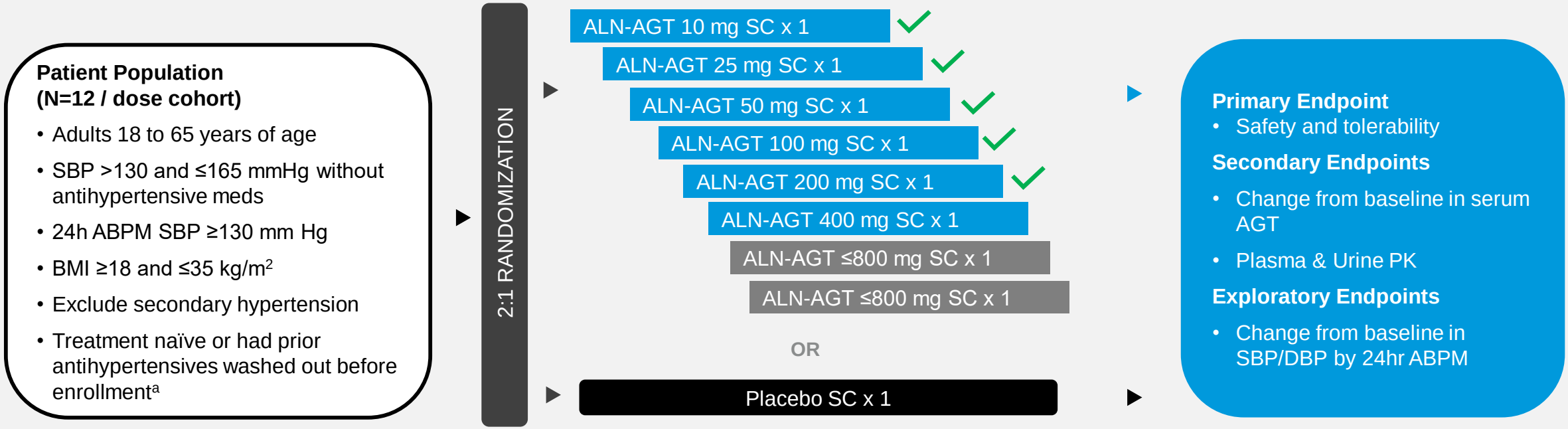
Potential Mechanistic Advantages

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

AGT, angiotensin; BP, blood pressure; q3M; every 3 months; siRNA, small interfering ribonucleic acid

ALN-AGT01 First-in-Human Single Ascending Dose Study

- A total of 60 patients with hypertension completed treatment as of 16-September-2020
- Patients received either placebo (n=4 per cohort) or ALN-AGT01 (n=8 per cohort)
- Study conducted in outpatient setting with usual activity and dietary sodium intake



- Additional cohorts planned to evaluate the use of ALN-AGT01:
  - Controlled salt intake: tolerability in salt depletion, recovery of BP with high salt
  - Obese patients: PK/PD and effect of ALN-AGT01 on BP and body composition
  - Addition of ARB in background of ALN-AGT01: safety and tolerability

✓ = completed cohorts
■ = optional dose cohorts

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

ABPM, ambulatory blood pressure monitoring; ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous

Demographics and Baseline Characteristics

		Placebo (N=20)	ALN-AGT01 Dose Cohort				
			10 mg (N=8)	25 mg (N=8)	50 mg (N=8)	100 mg (N=8)	200 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)
Gender	**Male**	9	7	2	7	3	5
	Female	11	1	6	1	5	3
Race	**White**	14	6	4	3	4	6
	Black	5	1	4	4	2	2
	Asian	0	1	0	0	2	0
	Other	1	0	0	1	0	0
Blood Pressure	**24h ABPM SBP median (range)**	141 (126,153)	139 (130, 147)	140 (132, 157)	135 (113, 144)	136 (131, 152)	139 (129, 154)
	24h ABPM DBP median (range)	87 (72-102)	83 (76, 93)	91 (75, 103)	84 (74, 91)	86 (80, 90)	83 (75, 95)

PRIMARY ENDPOINT: SAFETY & TOLERABILITY

ALN-AGT01 Was Generally Well-Tolerated Supporting Continued Development

Patients Reporting an Adverse Event (AE), N (%)	Placebo (N=20)	10 mg (N=8)	25 mg (N=8)	50 mg (N=8)	100 mg (N=8)	200 mg (N=8)
At least 1 Adverse Event	17	5	7	6	7	7
At least 1 Serious Adverse Event	1	0	0	0	0	1
At least 1 Severe Adverse Event	1	0	0	0	0	1

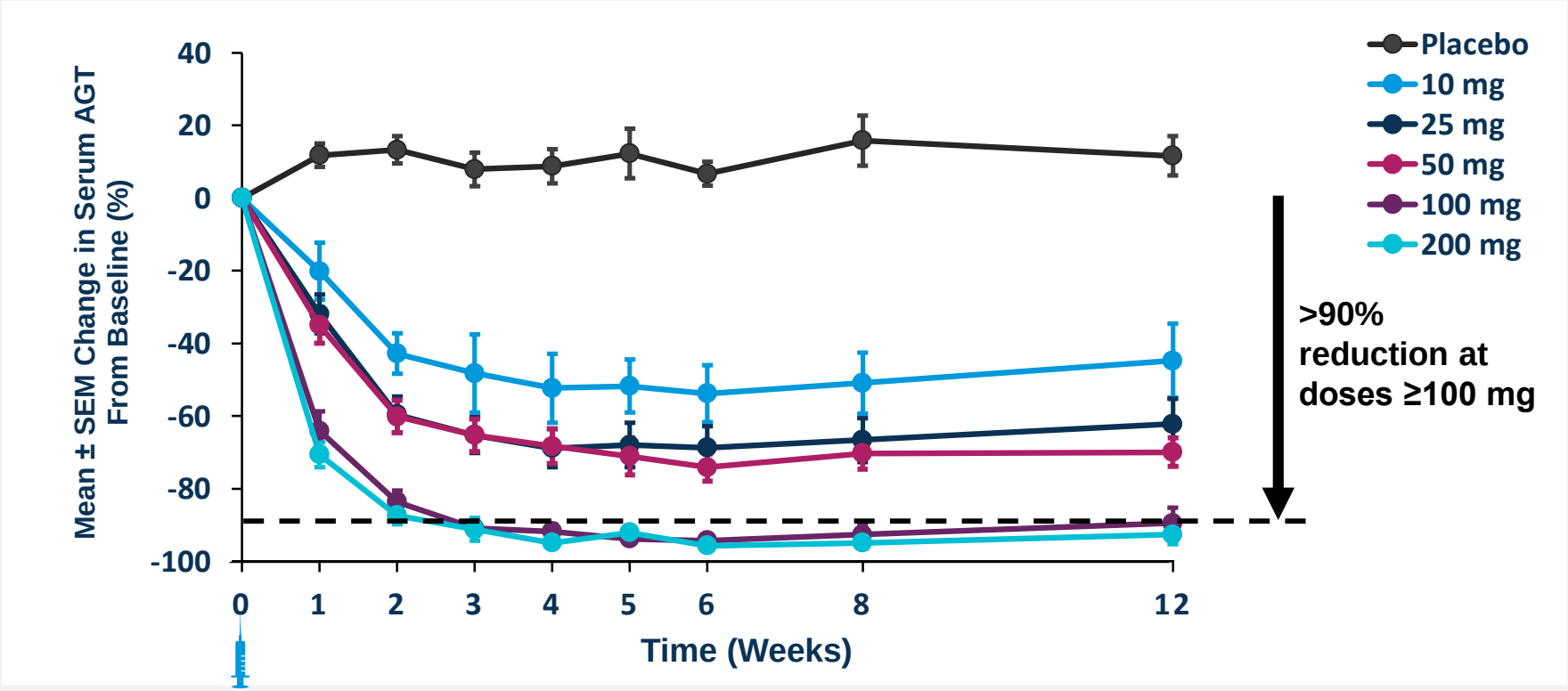
- Most AEs mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal
- No treatment-related Serious AEs (SAEs)
  - Severe and serious AE of prostate cancer reported in 1 patient who received 200 mg ALN-AGT01, based upon a biopsy that was performed in the screening period and reported as positive after dosing
- No patient has required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium
- 5 patients with injection site reactions, all mild and transient

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

SECONDARY ENDPOINT: DOSE-DEPENDENT AGT LOWERING

Durable Reduction of Serum AGT >90% Sustained for 3 Months After Higher Single Doses of ALN-AGT01

- Mean reduction in serum AGT at 8 weeks was 95 +/- 2% after 200 mg dose
- Maximum AGT reductions of 98% observed in individual patients after 200 mg dose



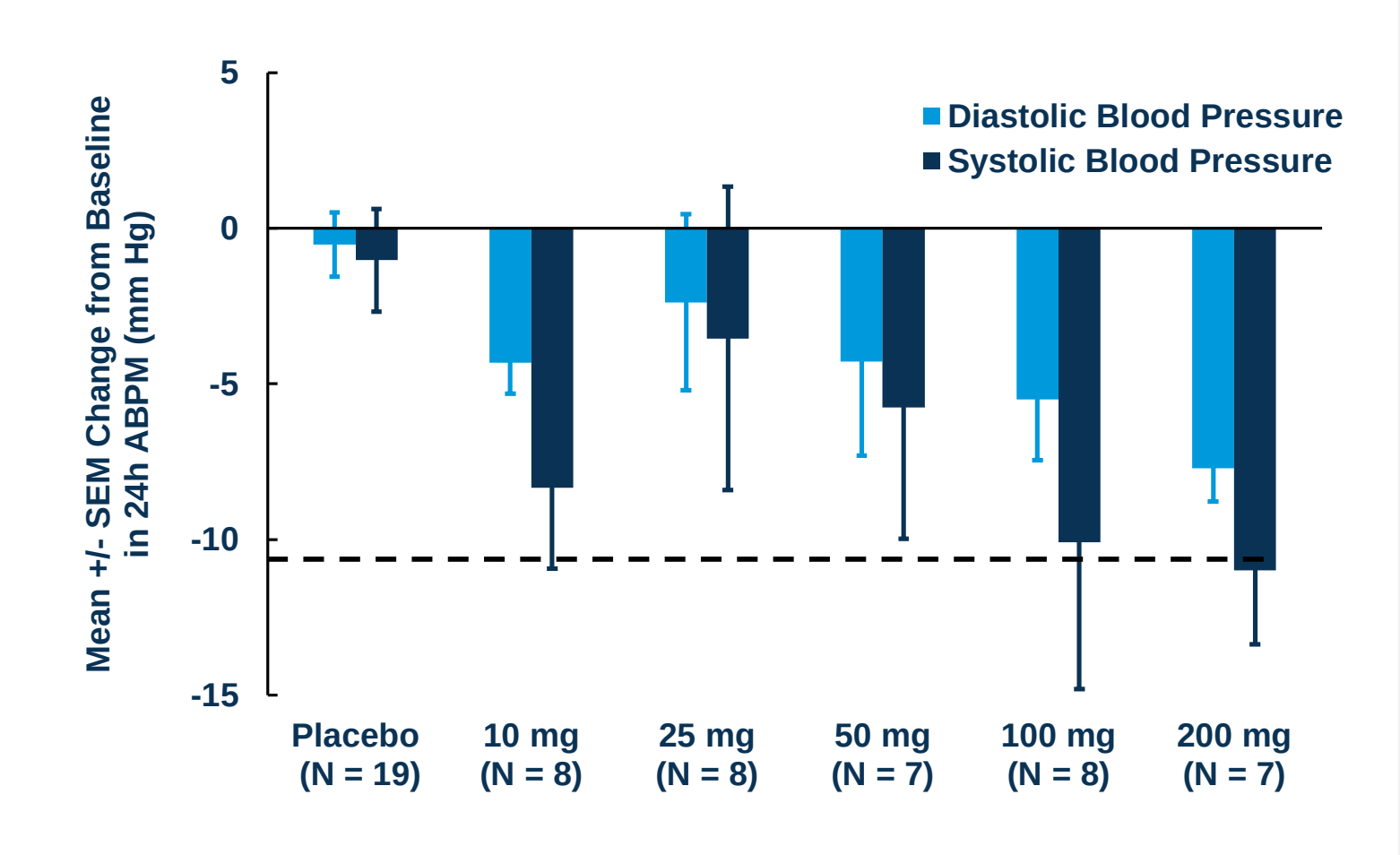
No. of patients:									
Placebo	20	20	20	20	19	17	18	19	20
10 mg	8	8	8	8	8	8	8	8	8
25 mg	8	8	8	8	8	8	8	8	8
50 mg	8	8	8	8	8	8	8	7	7
100 mg	8	7	8	8	8	8	8	8	7
200 mg	8	8	8	7	6	2	3	7	8

SEM, standard error of the mean

EXPLORATORY ENDPOINTS: DOSE-DEPENDENT REDUCTIONS IN SBP AND DBP

24h SBP Reduction >10 mm Hg at 8 Weeks After Higher Single Doses of ALN-AGT01

- Mean reductions in BP at 8 weeks were 11 +/- 2 mm Hg for systolic and 8 +/- 1 mm Hg for diastolic after 200 mg dose
- Maximum reductions of 19 mm Hg for systolic BP and 12 mm Hg for diastolic BP observed in individual patients after 200 mg dose



CONCLUSION

- **Single subcutaneous doses of investigational ALN-AGT01 were generally well-tolerated in patients with mild to moderate hypertension supporting continued development, with no treatment-related serious adverse events**
- **ALN-AGT01 led to a dose-dependent and durable reduction of serum AGT**
- **Serum AGT reductions >90% after higher single doses of ALN-AGT01 sustained for 3 months, supporting potential for infrequent dosing interval**
- **BP reductions mirror AGT knockdown, with >10 mm Hg reduction in 24h SBP observed at 8 weeks after single doses of 100 mg or higher**
- **This ongoing single ascending dose study will characterize maximum effect of ALN-AGT01 and potential durability of effect in lowering AGT beyond 3 months**

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