Safety, Pharmacodynamics, and Blood Pressure Effects of ALN-AGT, an RNA Interference Therapeutic Targeting Angiotensinogen, in a Randomized Single Ascending Dose Study of Hypertensive Adults

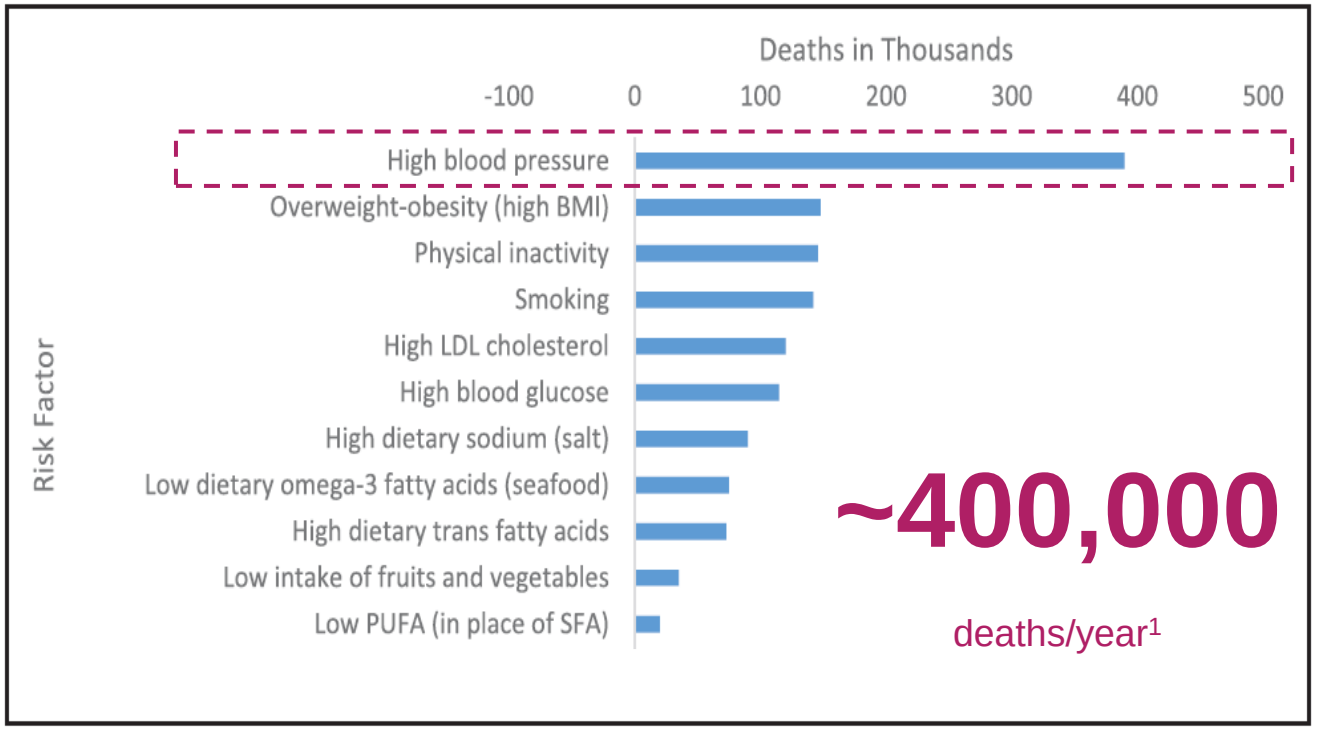
Stephen A Huang[1], Jorg Taubel[2], Giuseppe Fiore[3], David J. Webb[4], George L Bakris[5], Akshay S Desai[6], Yansong Cheng[1], Sagar Agarwal[1], Jamie Harrop[1], Huy V Nguyen[1], Jiandong Lu[1], Don Foster[1], Kenji Fujita[1]

[1]Alnylam Pharmaceuticals, Cambridge, MA, [2]Richmond Pharmacology and St. George's University of London, London, [3]Medicines Evaluation Unit Ltd., United Kingdom, [4]Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh, United Kingdom, [5]University Chicago Medicine, Chicago, IL, [6]Brigham Womens Hospital, Boston, MA

April 11-14, 2021 || European Society of Hypertension-International Society of Hypertension (ESH-ISH) Congress

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

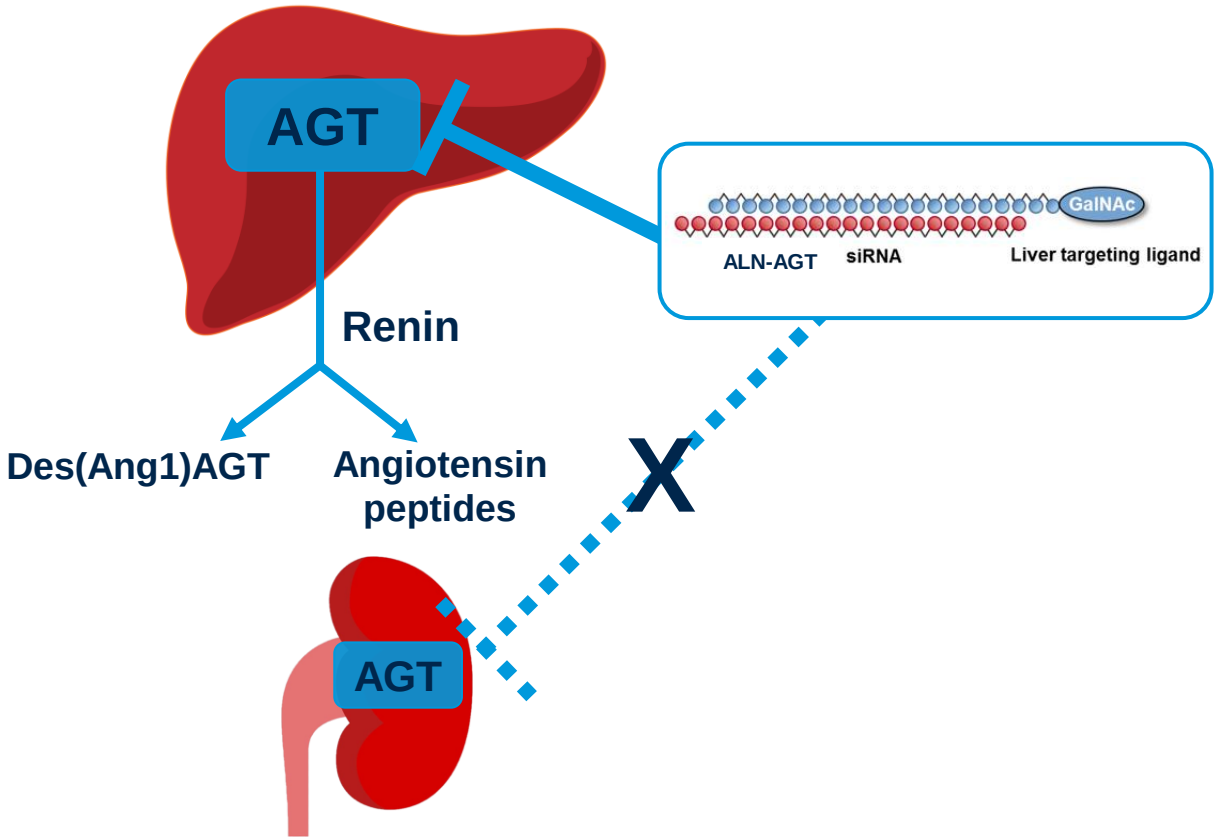
>50% of patients are nonadherent or suboptimally adherent to antihypertensive treatment

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-AGT Therapeutic Hypothesis

Liver-specific AGT Knockdown



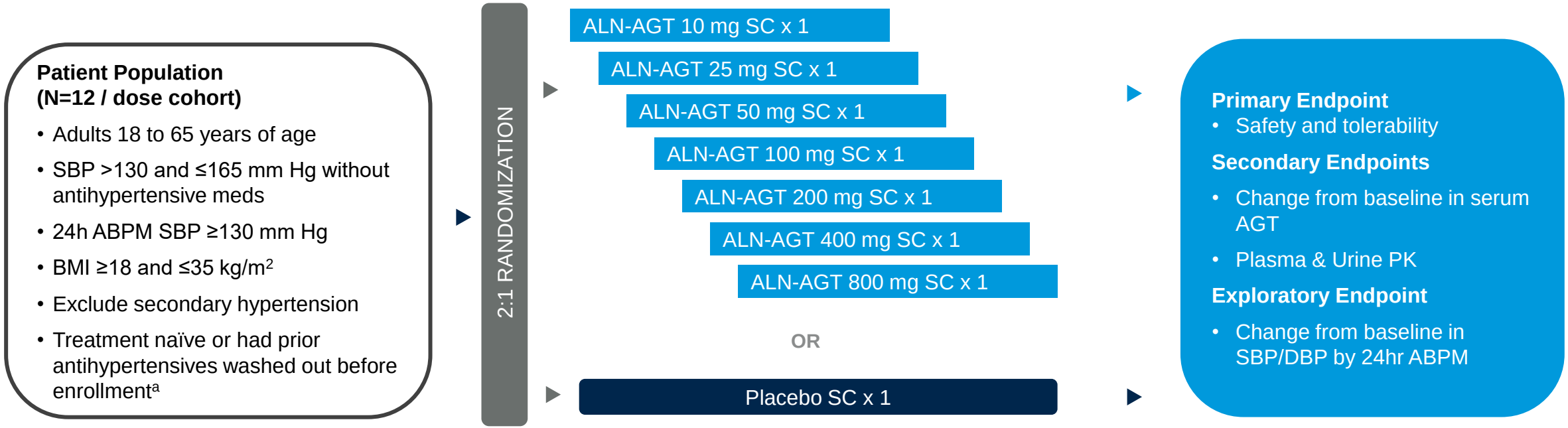
Potential Mechanistic Advantages

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

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

ALN-AGT 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

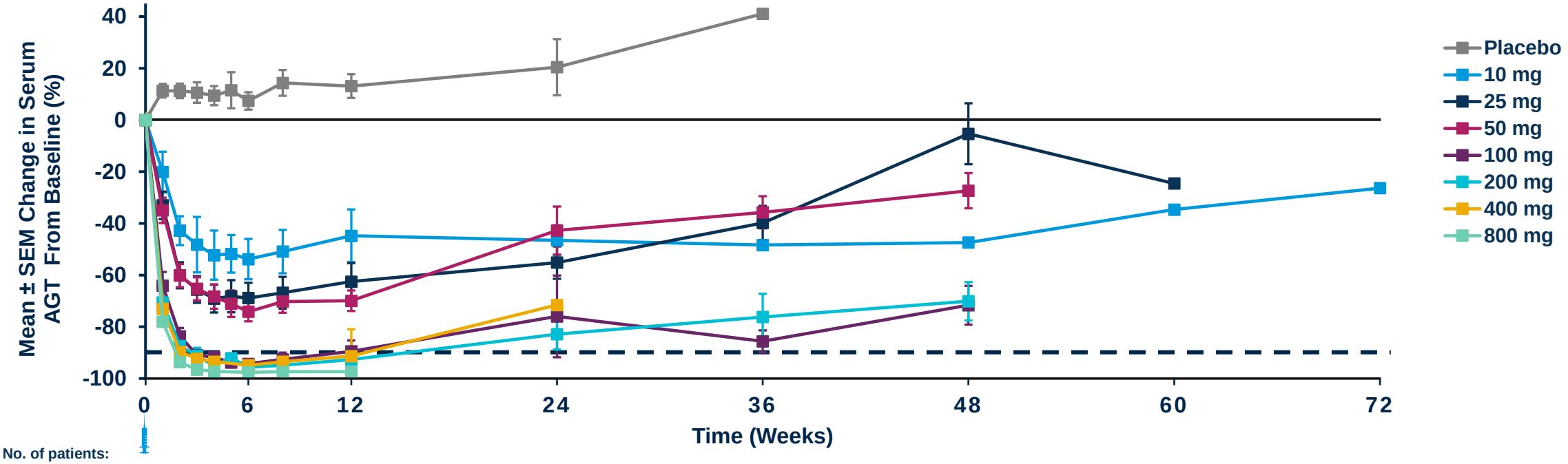
- Most AEs mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal
- No treatment-related Serious AEs (SAEs)
  - Severe and serious AE of prostate cancer reported in 1 patient who received 200 mg ALN-AGT, based upon a biopsy that was performed in the screening period and reported as positive after dosing
- 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 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
10 mg	8	8	8	8	8	8	8	8	8	5	2	1	1
25 mg	8	8	8	8	8	8	8	8	8	8	6	6	1
50 mg	8	8	8	8	8	8	8	7	7	7	4	2	0
100 mg	8	7	8	8	8	8	8	8	7	7	6	5	0
200 mg	8	8	8	7	6	2	3	7	8	8	4	5	0
400 mg	8	8	8	8	8	0	8	8	8	8	0	0	0
800 mg	8	8	8	7	8	0	8	8	8	0	0	0	0

AGT, angiotensinogen; SEM, standard error of the mean

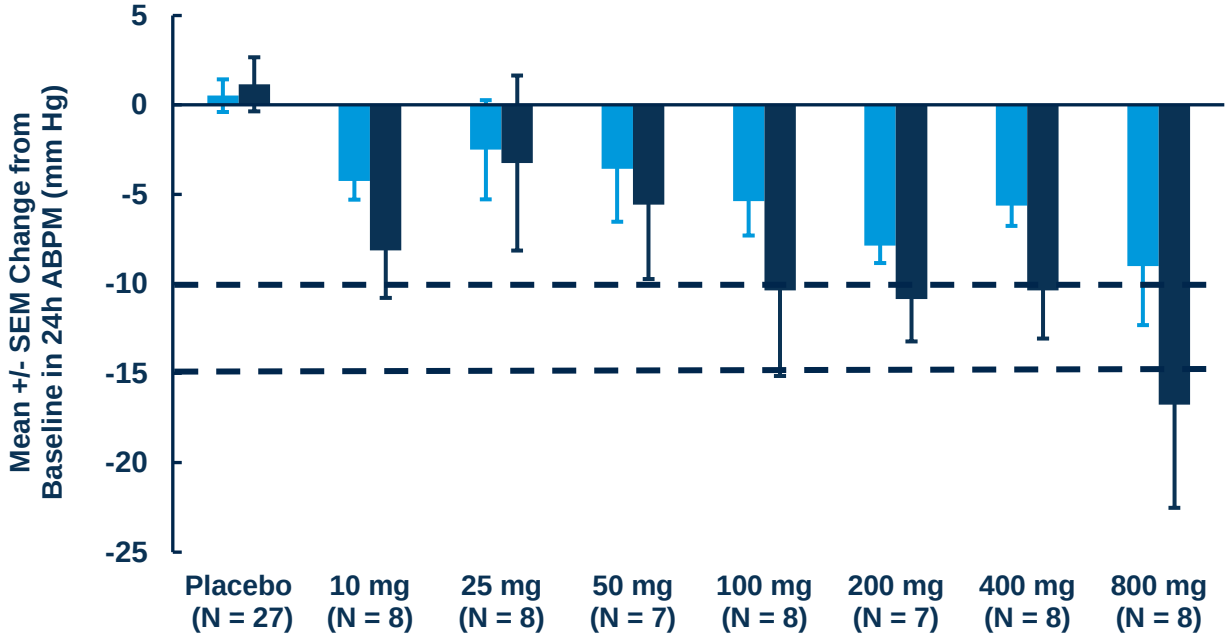
Exploratory Endpoint: Dose-Dependent Reductions in BP

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

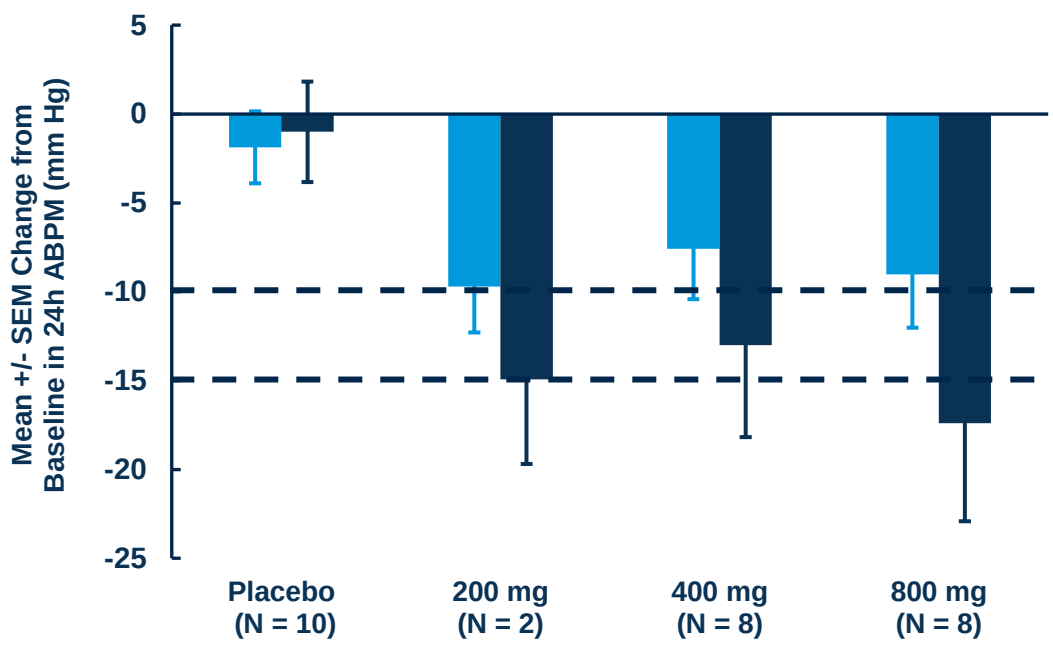
24h SBP Reduction >15 mm Hg at 8 Weeks After Single Doses of ALN-AGT 800 mg

- 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

*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

Conclusion

- Single subcutaneous doses of investigational ALN-AGT were generally well-tolerated in patients with mild to moderate hypertension supporting continued development
- ALN-AGT led to a dose-dependent and durable reduction of serum AGT
- Serum AGT reductions >90% sustained to 3 months after single doses of ALN-AGT ≥100 mg, supporting potential for infrequent dosing intervals of 3 or 6 months
- ALN-AGT led to >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
- Ongoing follow-up of this single ascending dose study will characterize potential durability of effect in lowering AGT and blood pressure beyond 3 months