Efficacy and Safety of Tonlamarsen in Patients with Uncontrolled Hypertension

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Disclosures: Dr. Laffin serves/served as a consultant or on steering committees for Arrowhead, AstraZeneca, Crispr Therapeutics, Diamedica, Eli Lilly, Kardigan, Madrigal, Medtronic, Mineralys, Novo Nordisk, Novartis, Recor, Retension, Ripple, Viking. He receives royalties from Belvoir Media Group, Elsevier, and Springer Nature.

Background

Tonlamarsen is an antisense oligonucleotide administered once-monthly via subcutaneous injection that suppresses hepatic angiotensinogen (AGT) production

AGT suppression reduces BP among patients taking 0 to 1 medications, however more data are needed in patients taking multiple medications including ACE-inhibitors and ARBs

No prior published data on the efficacy and safety of tonlamarsen

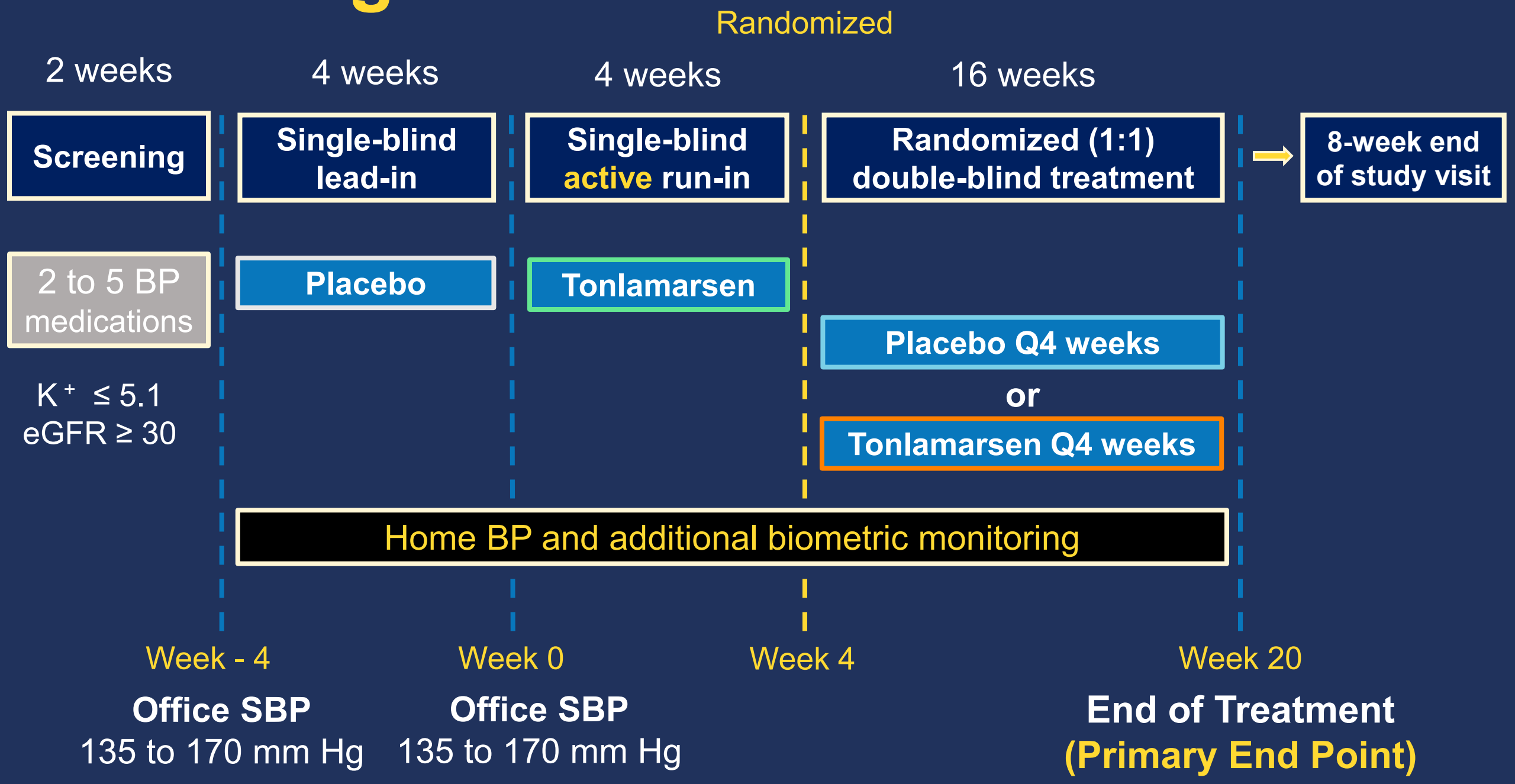
Objective

Assess the effect of 90 mg of tonlamarsen administered *every 4 weeks* on plasma AGT levels and SBP in participants with uncontrolled hypertension on ≥ 2 medications

Trial Design

- Multicenter (39 sites in the United States)
- Prospective
- Placebo lead-in
- Active run-in
- Randomized
- Double-blind
- Placebo-controlled
- Phase 2 trial

Trial Design



Co-Primary End Points*

Percent change in plasma AGT from Week 0 to Week 20

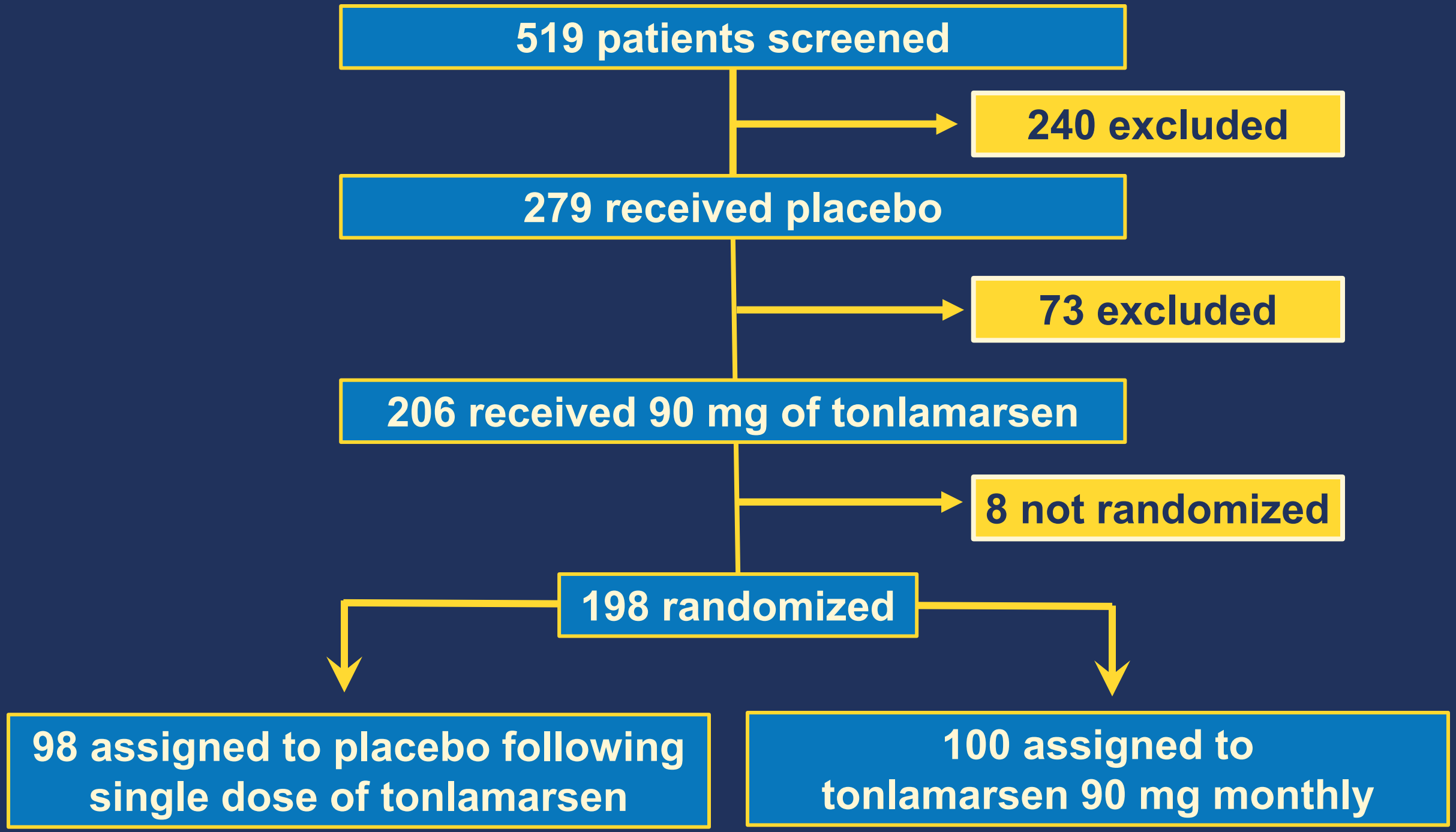
Change in office SBP from Week 0 to Week 20

*Multiplicity testing for the co-primary endpoints used Holm's step-down procedure to control the overall family-wise error rate at $\alpha = 0.05$

Secondary End Points*

- Proportion of participants with office SBP less than 130 mm Hg
- Change from Week 0 in mean self-assessed home SBP
- Proportion of participants with any daily home SBP greater than 150 mm Hg
- Change from Week 0 in office DBP

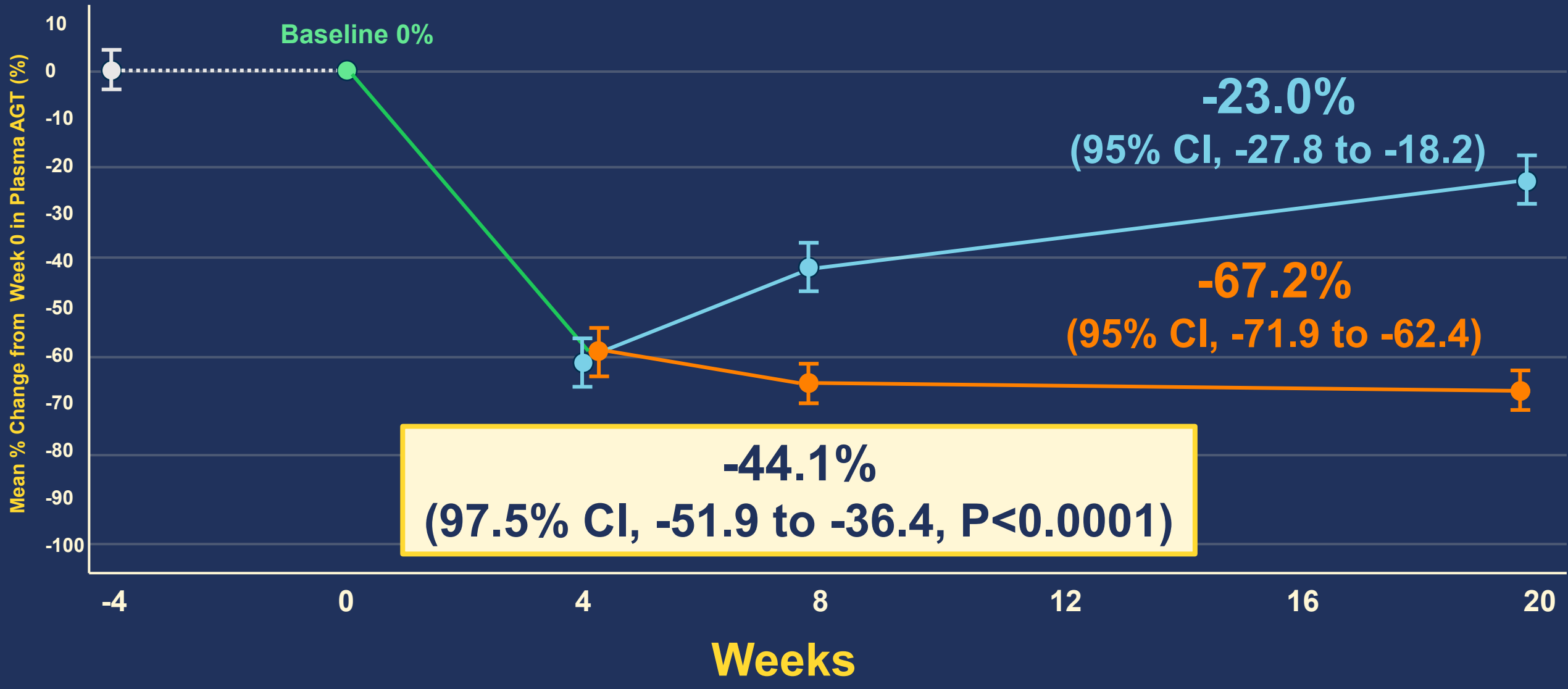
*Measured at/during Week 20 and controlled for multiplicity via a hierarchical testing approach


519 patients screened
240 excluded
279 received placebo
73 excluded
206 received 90 mg of tonlamarsen
8 not randomized
198 randomized
98 assigned to placebo following single dose of tonlamarsen
100 assigned to tonlamarsen 90 mg monthly

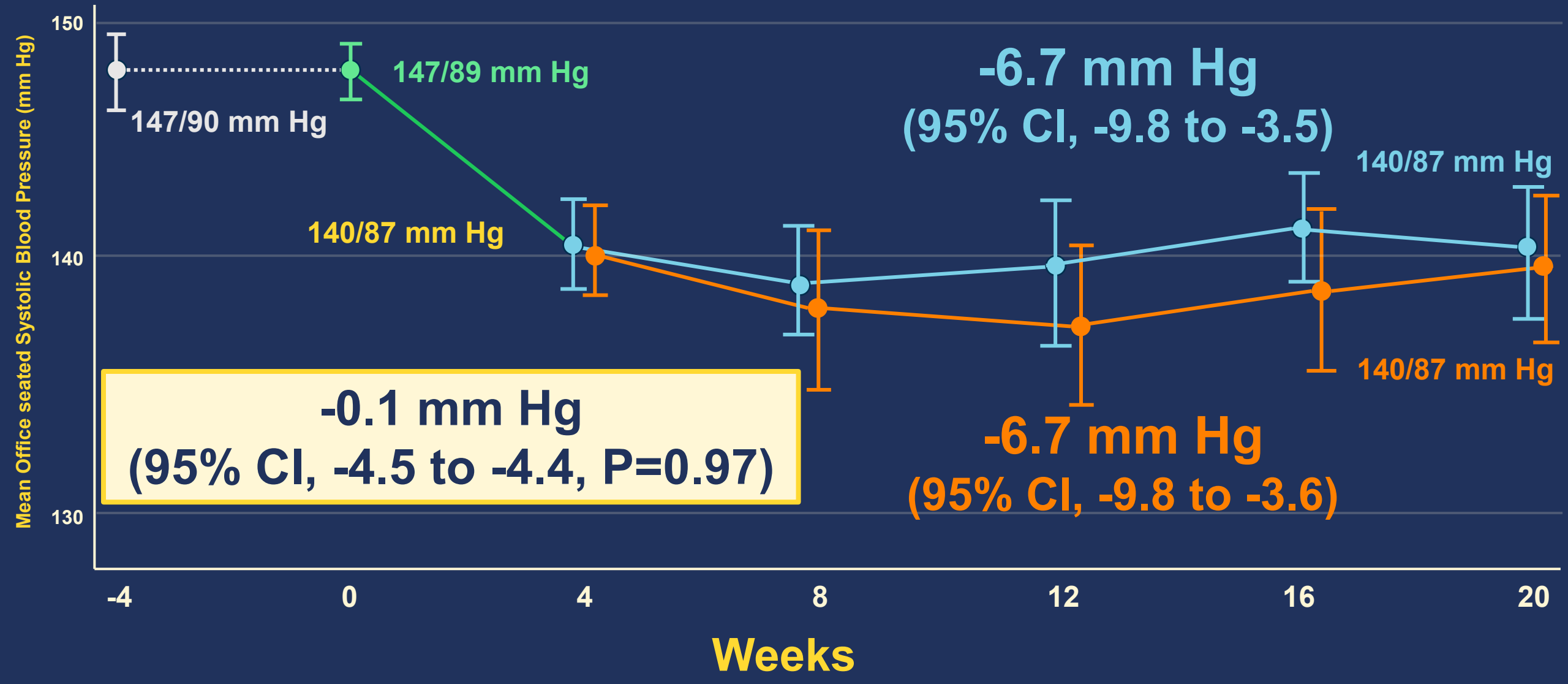
Participant Characteristics	Single Tonlamarsen Dose Followed by Placebo	Tonlamarsen Every 4 Weeks **(5 total doses)**
Age (years)	61	61
Women (%)	40%	42%
Black Race (%)	47%	50%
BMI (kg/m^2)	32	32
eGFR ($ml/min/1.73\ m^2$)	85	85
Office BP (Week 0)	148/89 mm Hg	146/90 mm Hg
Taking ACEi or ARB	84%	80%
≥3 BP medications	42%	39%

Continuous variables presented as means

Co-Primary End Point: Percent Change in AGT at Week 20



Co-Primary End Point: Change in Office SBP at Week 20



Key Secondary End Points

Between-group difference in the change from Week 0 to during Week 20 in Home SBP	**-3.1 (95% CI, -6.6 to 0.4)**
Between-group difference in the change from Week 0 to Week 20 in Office DBP	-0.8 (95% CI, -3.4 to 1.8)
Proportion with office SBP <130 mm Hg at Week 20	1.07 (OR, 95% CI, 0.55 to 2.08)
Proportion with any daily avg home SBP ≥ 150 mm Hg during Week 20	0.90 (OR, 95% CI, 0.46 to 1.76)

Tonlamarsen every 4 weeks was lower

Adverse Events	Single Tonlamarsen Dose Followed by Placebo	Tonlamarsen Every 4 Weeks (5 total doses)
Any serious AE	2%	5%
Hypotension	0%	1%
Serum Potassium > 5.5 mmol/L	2%*	0%
Decrease of > 30% in eGFR	3%	3%
Injection site reactions	3% (all) 1% (≥ Grade 2)	19% (all) 2% (≥ Grade 2)

* One participant had K > 5.5 mmol/L the day of first tonlamarsen dose (labs collected prior to drug administration)

Potential Explanations for AGT and BP Changes Observed in the KARDINAL Trial

#1

A single dose of tonlamarsen may result in sustained office BP reduction even as AGT suppression wanes

#2

Residual AGT suppression may have attenuated differences in office BP between treatment groups

#3

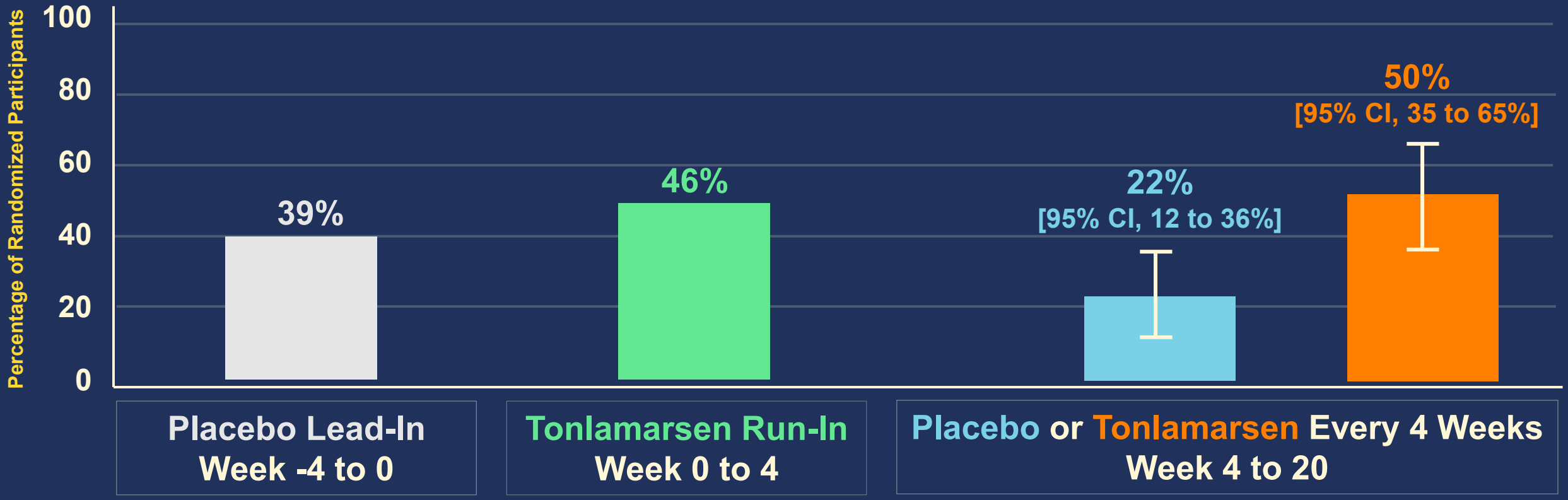
Improved adherence to background medications or additional regression to the mean in BP following placebo lead-in cannot be excluded

Study Limitations

- Lack of a placebo-only comparator arm
- Unexpected duration of AGT suppression
- Size and trial duration

Exploratory End Point

No Home SBP ≥ 150 mm Hg During Specified Treatment Period



Future Directions

KARDINAL - ASH (Acute Severe Hypertension)

Patients recently hospitalized with:

>180 mm Hg SBP or > 110 mm Hg DBP

Simultaneously Published in

JACC

Conclusions

90 mg of tonlamarsen monthly for a total of 5 months lowered plasma AGT more than a single dose of tonlamarsen and subsequent monthly placebo.

Similar office SBP lowering was observed between treatment groups despite partial recovery of plasma AGT.

Interpretation complicated by unanticipated persistence of AGT suppression after a single tonlamarsen dose, necessitating additional placebo-controlled trials without an active run-in.

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