#AHA23

EFFECT OF ION904, AN ANTISENSE INHIBITOR OF ANGIOTENSINOGEN PRODUCTION: RESULTS OF PHASE 1 AND PHASE 2 PILOT STUDIES

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DISCLOSURES

Erin Morgan is an employee of Ionis Pharmaceuticals, Inc

ION904 is an investigational study drug

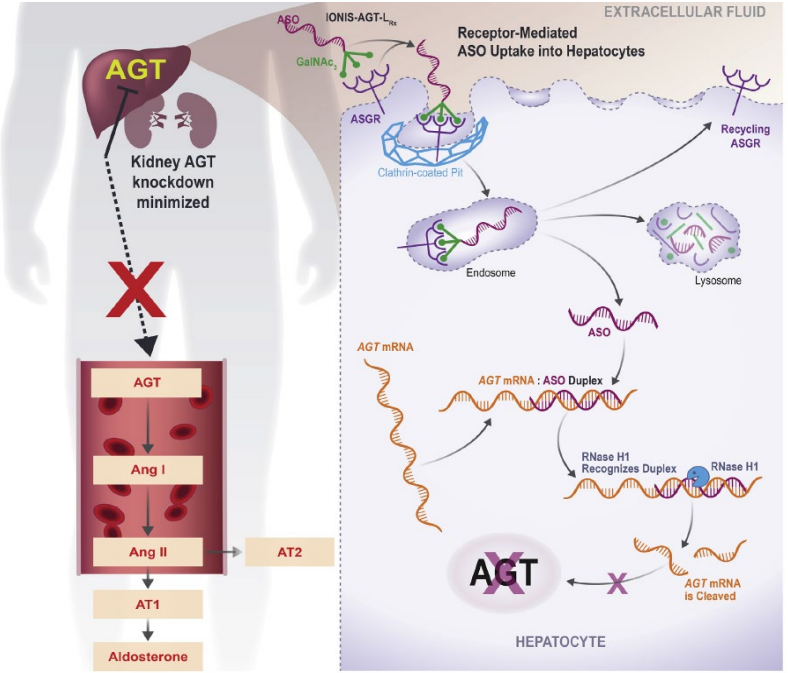
OBJECTIVE

We aimed to develop a more potent and durable ASO targeting Angiotensinogen (AGT)

Prior compound reached 67% AGT lowering with weekly dosing (Morgan *et al*, JACC Basic to Translational Science 2022

ION904 IS HEPATOCYTE-TARGETED ASO INHIBITING THE RAAS PATHWAY

Angiotensinogen Primarily Synthesized in the Liver



ION904 is a GalNAc-conjugated ASO **targeting AGT mRNA** in hepatocytes and designed to **allow monthly dosing**

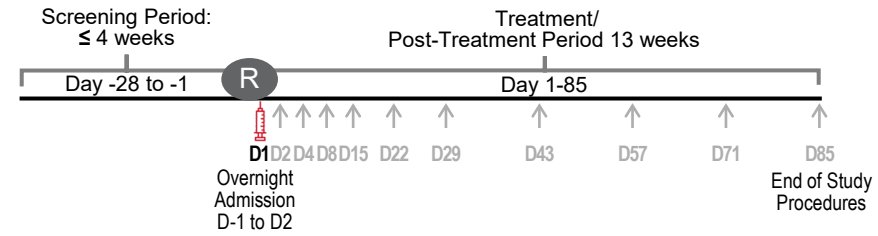
RNA therapeutic approach targets AGT, the **upstream RAS substrate** of angiotensin I-II and aldosterone, limiting the potential for angiotensin/aldosterone breakthrough

Targeting liver AGT **minimizes renal side effects observed with RAASi standard of care** (hyperkalemia, renal dysfunction, acute renal failure, hypotensive events)

STUDY DESIGNS FOR ION904 STUDIES

(HV and Mild HTN Patients)

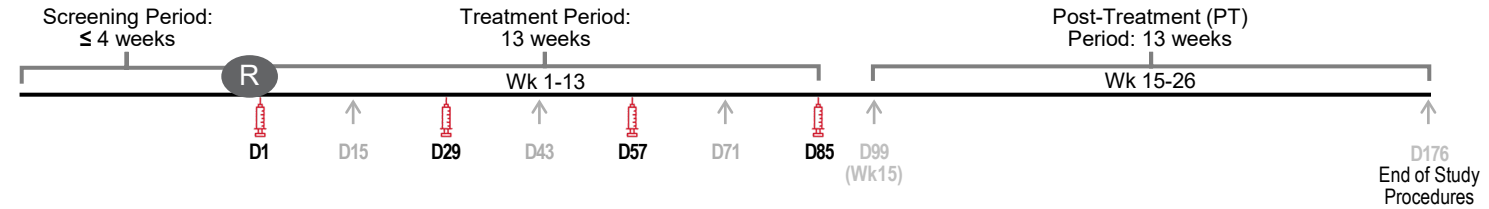
CS1



Healthy Volunteers

ION904 mg	N
PBO	10
10	6
30	6
60	6
90	6
120	6
Total	**40**

CS2



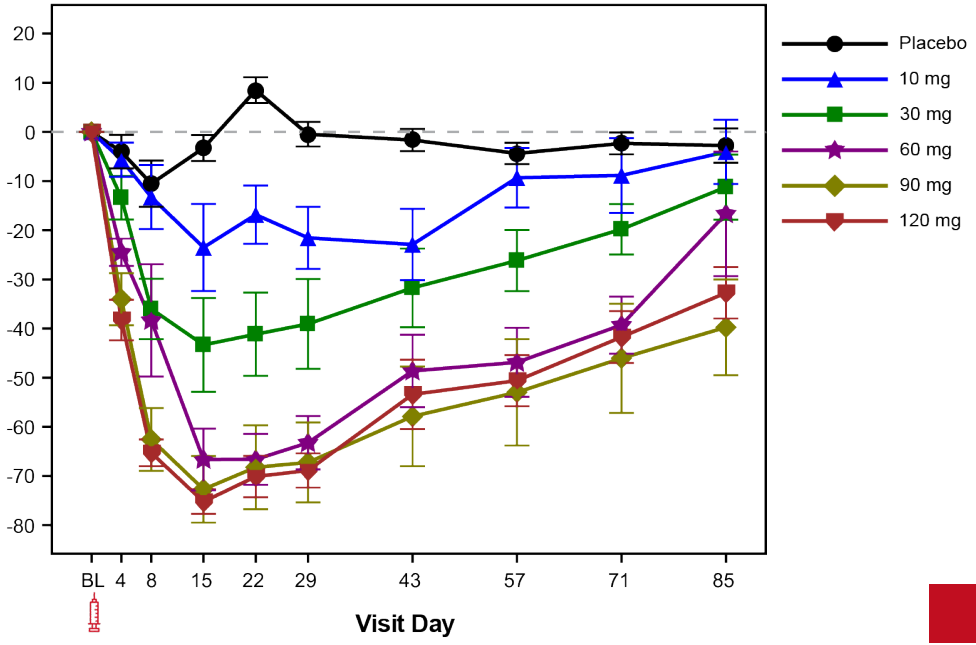
ION904 mg	N
PBO	12
30	11
60	13
90	12
Total	**48**

HTN patients (SBP 130-170 mmHg) on 1 + meds
Key BL Characteristics:
BP 145/84, 35% F, 31% Non-White, 88% CVD Risk Factors, 42% T2D, 50% Obese, 100% eGFR >45, 63% were on ACEi/ARB

Key:
↑ Safety visit (vitals, labs, AE, CM)
Dosing and safety visit

PH1: SINGLE DOSES OF ION904 DEMONSTRATED ROBUST AND SIGNIFICANT AGT REDUCTIONS WITH SUPPRESSION OF RAAS METABOLITES

AGT (nmol/L) Mean % Change (SEM)
Per Protocol Set



Mean % Change from Baseline to 1 Month (Day 29)

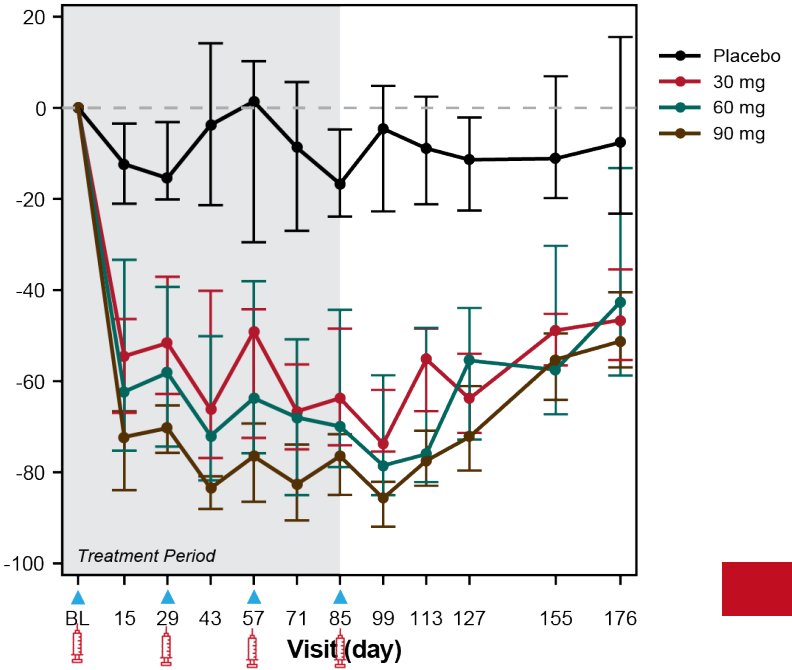
RAAS Metabolite	PBO	ION904 90 mg	ION904 120 mg
N	10	6	6
AGT (nmol/L)	-1%	-67%**	-69%**
ANGI (pmol/L)	+80%	-4%	-9%
ANGII (pmol/L)	+56%	-17%	-9%
Aldosterone (pmol/L)	+28%	-46%	-13%

**p=<0.001

90% AGT Reductions Observed in Individuals

PH2: MULTIPLE, MONTHLY DOSES OF ION904 IN HTN PTS RESULTED IN SIGNIFICANT AND SUSTAINED AGT REDUCTIONS

AGT (nmol/L) Median (Q1-Q3) % Change Per Protocol Set



AGT % Change From Baseline to Day 99 (Wk 15) Primary Endpoint

	PBO	ION904 30 mg	ION904 60 mg	ION904 90 mg
N	10	9	9	8
Mean Change	-6%	-71%**	-70%**	-79%*
Median Change	-5%	-74%	-79%	-86%

*p=0.001
**p=<0.001

Study Not Powered for Significant SBP Reductions

ION904 DOSING RESULTS IN FAVORABLE SAFETY AND TOLERABILITY PROFILE

- Acceptable safety profile demonstrated in healthy volunteers and uncontrolled mild HTN patients with comorbidities (e.g. obese, type 2 diabetes) on ACE or ARB therapy
- No deaths, no related SAEs, and no stopping rules met (hepatic, renal, platelets)
- The most frequently reported TEAEs were mild to moderate;
  - Injection site erythema (0% placebo, 19.4% ION904)
  - Headache (8.3% placebo, 11.1% ION904)
  - Injection site pruritus (0% placebo, 8.3 % ION904)
- No hepatic (ALT or AST > 3X ULN), renal (creatinine or GFR), or thrombocytopenia signals observed
- No signals observed for hypotension, renal dysfunction, or hyperkalemia

CONCLUSION

- ION904 has been administered in 2 completed pilot studies in Healthy Volunteers and mild HTN patients
- ION904 achieved AGT median reductions of 86% at the 90 mg dose
- Monthly administration of ION904 demonstrated
  - significant and potent plasma AGT reductions
  - favorable safety and tolerability profile
- Results support development in hypertension and heart failure

THANK YOU





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A LARGER PROPORTION OF ION904 TREATED PATIENTS DEMONSTRATED SBP LOWERING >10 MMHG

Proportion of Patients with SBP Response

SBP reduction at Day 99	PBO (n=10)	ION904 treated (n=26)
> 0 mmHg, n (%)	4 (40)	18 (69)
>10 mmHg, n (%)	3 (30)	11 (42)

No Hypotension Signal Observed

Study Not Powered for Significant SBP Reductions

Effect of ION904, An Antisense Inhibitor of Angiotensinogen Production: Results of Phase 1 and Phase 2 Pilot Studies