Safety and Tolerability of ALN-AGT, an RNA Interference Therapeutic Targeting Hepatic Angiotensinogen Synthesis, in Hypertensive Patients during Sodium Depletion or Irbesartan Coadministration

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Zilebesiran (ALN-AGT) is under investigation for the treatment of hypertension.

Disclosures

Akshay Desai

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Biofourmis: Consulting fees
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Cytokinetics: Consulting fee
DalCor Pharmaceuticals: Consulting fees
Lexicon Pharmaceuticals: Consulting fees
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Merck: Consulting fees
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Vifor Pharma: Consulting fees
Regeneron Pharmaceuticals: Consulting fees
Sun Pharma: Consulting fees
Verily: Consulting fees

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Background and Rationale

Hypertension

- Hypertension is a leading cause of mortality and morbidity worldwide[1-5]
- Despite effective antihypertensives, hypertension is uncontrolled in ~50% of patients and >50% of patients are non- or suboptimally adherent[1-5]
- The RAAS has a demonstrated role in BP regulation[6,7]
  - AGT is the most upstream precursor of the RAAS[7]

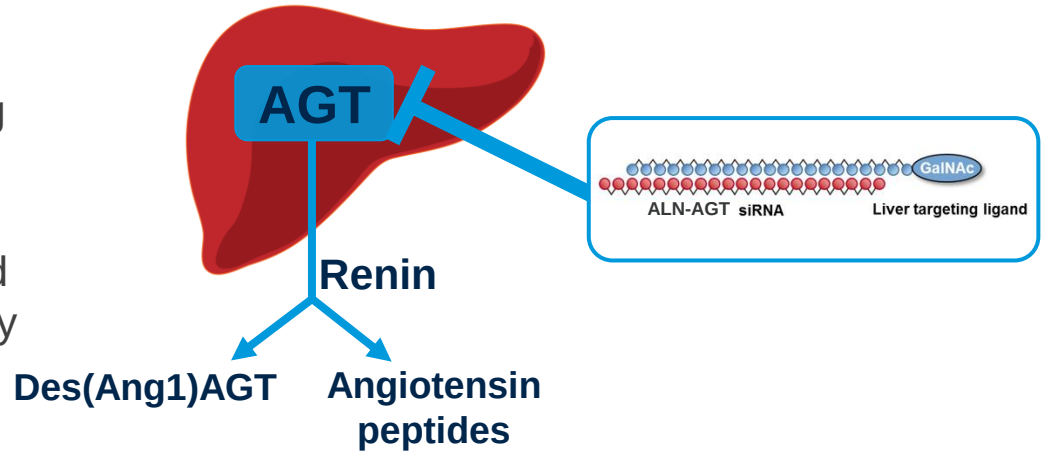
Zilebesiran

- Zilebesiran (ALN-AGT), a SC administered RNAi therapeutic targeting hepatic AGT synthesis is under investigation for the treatment of hypertension
- Previous presentations demonstrated that zilebesiran reduced BP and was generally well tolerated in a Phase 1, single ascending dose study of patients with hypertension[8]
  - Dose-dependent reductions in serum AGT were observed

Objective

- To assess the safety and tolerability of zilebesiran during sodium deprivation or irbesartan coadministration in a Phase 1 study

Liver-specific AGT Knockdown



AGT, angiotensinogen; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system; RNAi, ribonucleic acid interference; SC, subcutaneous

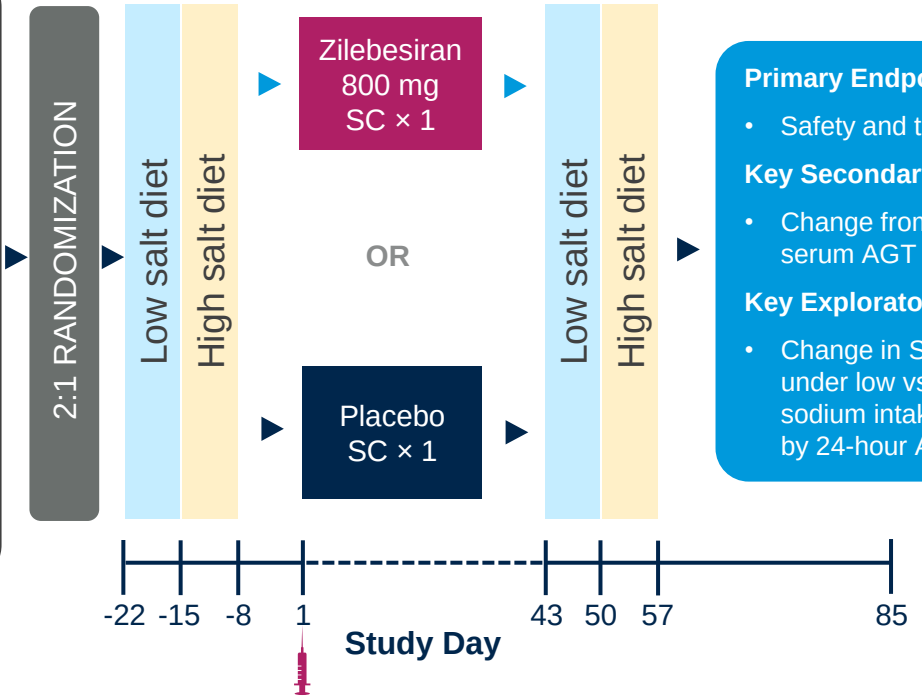
1. McClellan M et al. *Circulation* 2019;139:e44–e54; 2. Zhou B et al. *Nat Rev Cardiol* 2021;18:785–802; 3. Burnier M & Egan BM. *Circ Res* 2019;124:1124–1140; 4. Kotseva K et al. *Eur J Prev Cardiol* 2016;23:636–648; 5. Yoon SS et al. *NCHS Data Brief* 2015;1–8; 6. Te Riet L et al. *Circ Res* 2015;116:960–975; 7. Kumar R et al. In: Mann D, ed. *Heart Failure: A Companion to Braunwald's Heart Disease,* 2nd Edition. Saunders Press; 2010:134–151. 8. Desai et al. Oral presentation at European Society of Hypertension Congress 2021; Virtual.

Assessing Tolerability of Zilebesiran During Sodium Deprivation

- Randomized, double-blind, placebo-controlled study
- Two-week dietary sub-protocol[a] with varying sodium consumption, to test for potential salt-sensitive BP responses

Patient Population (N=12)

- Adults 18-65 years of age
- SBP >130 and ≤165 mmHg without antihypertensive medications
- 24-hour SBP ≥130 mmHg
- BMI ≥18 and ≤35 kg/m^2
- Secondary hypertension excluded
- Treatment naïve or had prior antihypertensives washed out for ≥2 weeks before screening



Primary Endpoint

- Safety and tolerability

Key Secondary Endpoint

- Change from baseline in serum AGT

Key Exploratory Endpoint

- Change in SBP/DBP under low vs high sodium intake assessed by 24-hour ABPM

Baseline Demographics and Characteristics

Characteristic		Placebo (N=4)	Zilebesiran (N=8)
Age, years; median (range)		52 (35–62)	60 (49–64)
Gender	Male (%)	3 (75)	6 (75)
Race	White	3	5
	Black	1	2
	Asian	0	1
Blood Pressure (24-hour ABPM, mmHg)	SBP median (range)	147 (133–151)	138 (129–150)
	DBP median (range)	98 (87–103)	88 (77–93)

[a]Low salt diet (0.23 g sodium per day) pre-dose (Day -22 to Day -15) and post-dose (Day 43 to Day 50). High salt diet (5.75 g sodium per day) pre-dose (Day -15 to Day -8) and post-dose (Day 50 to Day 57)
ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SC, subcutaneous

Safety and Tolerability in Low/High Salt Diet

Zilebesiran Was Generally Well Tolerated With No Drug-Related SAEs

- All AEs mild in severity and resolved without intervention
- No deaths or SAEs were reported
- No AEs leading to study withdrawal
- No AEs of injection site reaction or hypotension
- No patient required intervention for low blood pressure, including during the sodium deprivation period
- No clinically significant elevations in ALT, serum creatinine or serum potassium in zilebesiran group were reported
- One patient receiving placebo had transient ALT elevation >3x ULN attributed to alcohol consumption

Summary of Adverse Events

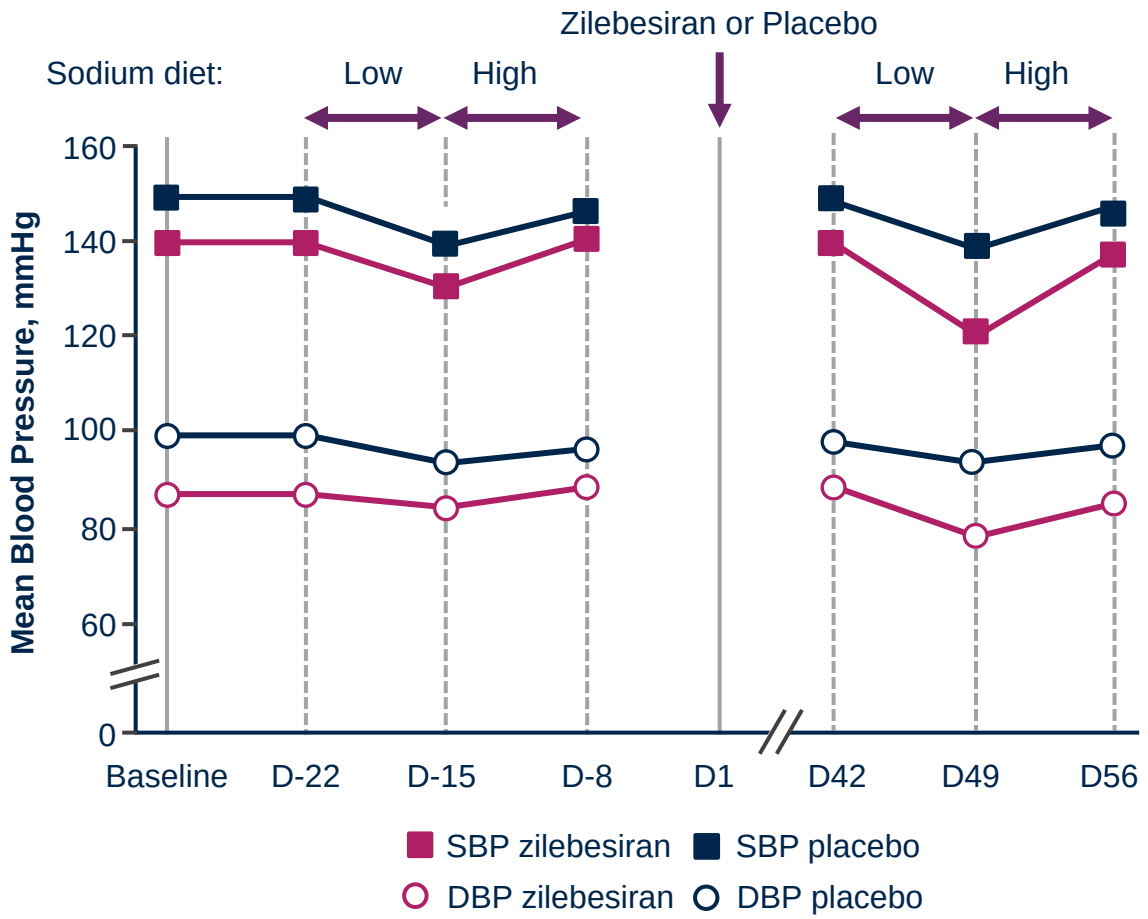
Number of Patients with at Least One Event, n	Placebo (N=4)	Zilebesiran (N=8)
Adverse Event	4	3
Serious Adverse Event	0	0
Severe Adverse Event	0	0

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event; ULN, upper limit of normal.
Data transfer date: May 28, 2021 (all patients completed low- and high-salt diets before data transfer). Safety reported from start of study drug to day 85.

Changes in 24-Hour BP in Low/High Salt Diet

- Zilebesiran 800 mg resulted in a reduction in serum AGT levels of >90%, sustained between Week 2 and Week 12 (data not shown)
- A reduction in 24-hour SBP/DBP was observed pre-dose for all patients following a low-salt diet; BP increased upon switching to a high-salt diet
- Post-dose, BP changes were more profound following a low-salt diet for patients receiving zilebesiran vs patients receiving placebo; a high-salt diet modulated the BP lowering effect of zilebesiran

Changes in ABPM during Modified Sodium Intake

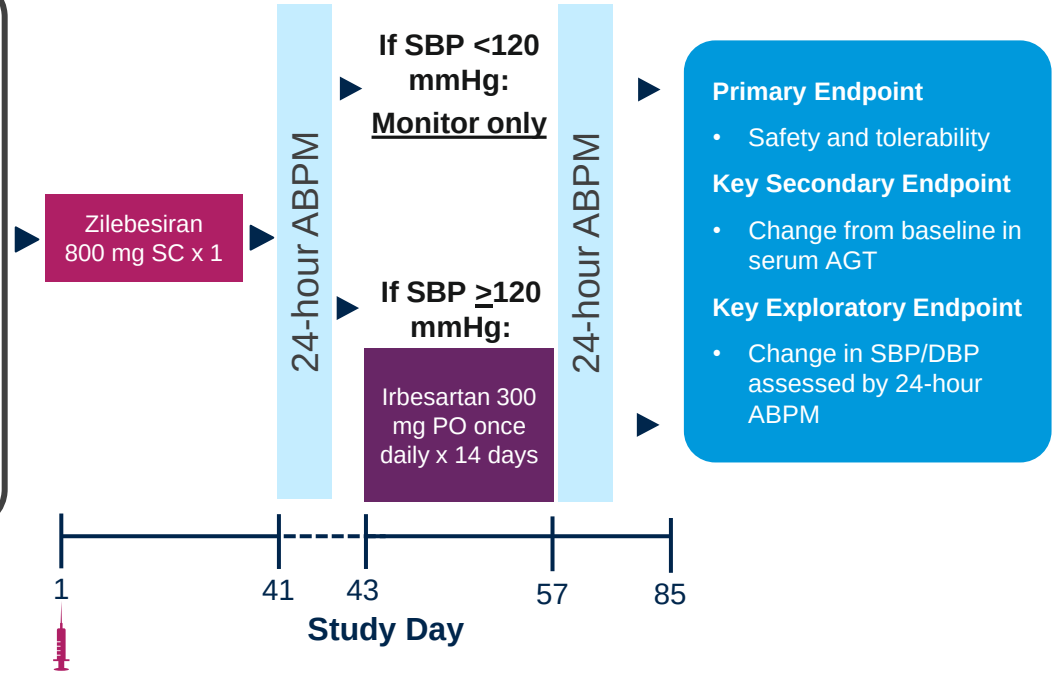


AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

Assess Tolerability of Zilebesiran During Irbesartan Coadministration

- All patients received single-dose open-label zilebesiran 800 mg SC
- On Day 41, patients with 24-hour mean SBP ≥120 mmHg (N=10) proceeded to receive irbesartan from Day 43 to Day 57

Patient Population (N=16)
- Adults 18-65 years of age
- SBP >135 and ≤165 mmHg without antihypertensive medications
- 24-hour ABPM SBP ≥130 mmHg
- BMI ≥18 and ≤50 kg/m^2
- Secondary hypertension excluded
- Treatment naïve or had prior antihypertensives washed out for ≥2 weeks before screening



Primary Endpoint
- Safety and tolerability

Key Secondary Endpoint
- Change from baseline in serum AGT

Key Exploratory Endpoint
- Change in SBP/DBP assessed by 24-hour ABPM

Baseline Demographics and Characteristics

Characteristic		Zilebesiran (N=6)	Zilebesiran + irbesartan (N=10)
Age, years; median (range)		56 (44–58)	56 (42–64)
Gender, n (%)	Male	5 (83)	3 (30)
Race, n	White	6	4
	Black	0	3
	Asian	0	1
	Other	0	2
Blood Pressure (24-hour ABPM, mmHg)	SBP median (range)	135 (124–141)	146 (135–158)
	DBP median (range)	83 (78–98)	89 (76–99)

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; DBP, diastolic blood pressure; PO, by mouth; SBP, systolic blood pressure; SC, subcutaneous

Safety and Tolerability With and Without Irbesartan Coadministration

Zilebesiran Was Generally Well Tolerated, With No Drug-Related SAEs

	Period 1 (Before Day 43)		Period 2 (On or After Day 43)	
Number of Patients with at Least One Event, n	**Zilebesiran only (N=6)**	**Zilebesiran prior to irbesartan (N=10)**	**Zilebesiran only (N=6)**	**Zilebesiran + irbesartan (N=10)**
Adverse Event	4	5	3	3
Serious Adverse Event	0	1	0	0
Severe Adverse Event	0	0	0	0

- All AEs were mild in severity
- 1 SAE (mild) of acute anemia in the irbesartan add-on group considered not related to study drug
  - A complication of esophagogastroduodenoscopy with biopsy performed during screening prior to dose of zilebesiran
- No deaths or AEs leading to study withdrawal
- No patient required intervention for low blood pressure
- There were no AEs of concern for hypotensive events during irbesartan coadministration, and no patient required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine or serum potassium were reported

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event
Data transfer date: 28 May 2021. Safety reported from start of study drug to day 85.

BP Further Reduced with Irbesartan Coadministration

- Reductions in serum AGT levels of >90% were achieved and sustained between Week 2 and Week 12 following a single dose of zilebesiran 800 mg alone (data not shown)
  - Coadministration of irbesartan 300 mg PO daily had no additional effect on serum AGT levels
- A single dose of zilebesiran 800 mg SC reduced both systolic and diastolic BP (Day 1−41)
- Daily coadministration of irbesartan for 2 weeks in patients with SBP ≥120 mmHg further reduced systolic and diastolic BP (Day 43−57)

	Δ24h SBP mmHg; mean (SEM)		Δ24h DBP mmHg; mean (SEM)	
Time Period	**Zilebesiran only (N=6)**	**Zilebesiran prior to irbesartan (N=10)**	**Zilebesiran only (N=6)**	**Zilebesiran prior to irbesartan (N=10)**
Day 1 (Baseline) to Day 41	-22.0 (2.9)	-7.7 (2.5)	-14.3 (2.3)	-3.3 (1.0)
		With irbesartan coadminstration		**With irbesartan coadminstration**
Day 43 to Day 57	0.4 (2.9)	-6.4 (3.1)	-0.5 (1.6)	-3.2 (1.9)

AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; PO, by mouth; SBP, systolic blood pressure; SC, subcutaneous; SEM, standard error of the mean.

Conclusions

- Single subcutaneous doses of investigational zilebesiran 800 mg were generally well-tolerated in patients with mild to moderate hypertension, with no AE of hypotension or clinically significant laboratory abnormalities reported during the low-salt diet or coadministration with irbesartan
- A high-salt diet modulated the BP-lowering effect of zilebesiran, providing early evidence that the standard intervention could be effective to treat potential hypotensive adverse events
- Coadministration of irbesartan with zilebesiran further reduced BP without clinically significant changes in serum creatinine or potassium levels
- Zilebesiran will be further investigated for the treatment of hypertension in a Phase 2 clinical study in patients with uncontrolled blood pressure despite standard-of-care antihypertensive treatment

Thank you to the patients, their families, investigators, study staff, and collaborators for their continued participation in the zilebesiran Phase 1 study

AE, adverse event; BP, blood pressure