Vutrisiran: Technetium Scintigraphy

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SUMMARY

- In the HELIOS-A study, technetium scintigraphy imaging was conducted in a planned cohort as one of the exploratory endpoints to assess cardiac amyloid involvement.[1]
- Cardiac uptake of ^{99m}Tc on scintigraphy imaging at Month 18 was reduced from baseline in the majority of evaluable patients following treatment with vutrisiran.[1]
- During the 18-month treatment period of HELIOS-A, vutrisiran demonstrated an acceptable cardiac safety profile, with the majority of AEs being mild or moderate in severity.[1,2]

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CLINICAL DATA

HELIOS-A Study

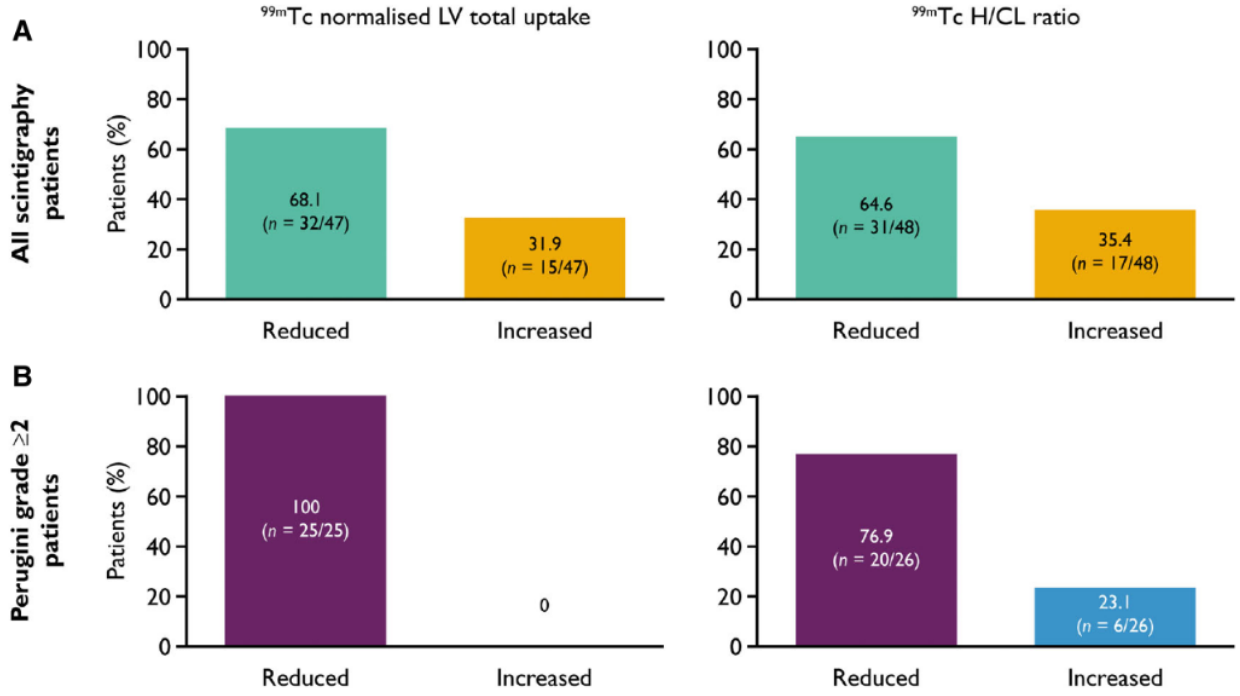
HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with the polyneuropathy of hATTR. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study (NCT01960348) as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[2]

At select sites, technetium scintigraphy was conducted as one of the exploratory endpoints to assess cardiac amyloid involvement at baseline and Month 18. Based on local practice for technetium scintigraphy, either ^{99m}Tc-DPD, ^{99m}Tc-PYP, or ^{99m}Tc-HMDP was used as the tracer.[1]

Planned Technetium Scintigraphy Cohort

Among 64 patients who received vutrisiran and underwent ^{99m}Tc scintigraphy at baseline, 47 patients had evaluable data at baseline and Month 18 for normalized LV total uptake. Of these 47 patients, 25 patients were Perugini grade ≥2 at baseline. Forty-eight patients had evaluable data at baseline and Month 18 for H/CL ratio. Of these 48 patients, 26 patients were Perugini grade ≥2 at baseline. Cardiac uptake of ^{99m}Tc on scintigraphy imaging at Month 18 was reduced from baseline in the majority of evaluable patients following treatment with vutrisiran (**Figure 1**). The clinical significance of this observation is not yet clear.[1]

Figure 1. Quantitative Assessments of Cardiac ^{99m}Tc Uptake at Month 18.[1]



Abbreviations: ^{99m}Tc = technetium; H/CL = heart to contralateral lung; LV = left ventricle; mITT = modified intent-to-treat.
Footnotes: Analysis includes vutrisiran-treated patients from mITT population with evaluable data at baseline and Month 18.
"Reduced" refers to a negative change (<0 increase) from baseline to Month 18. "Increased" refers to a >0 increase from baseline to Month 18.
From Garcia-Pavia et al.[1]

Among those who underwent ^{99m}Tc scintigraphy at baseline, 27 (42.2%), 2 (3.1%), 3 (4.7%), and 32 (50.0%) patients were Perugini grade 0, 1, 2, and 3, respectively. Of these 64 patients, 57 patients had evaluable data for Perugini grading at Month 18. A total of 55 (96.5%) patients with evaluable data were unchanged (n = 39, 68.4%) or experienced a reduction by ≥1 Perugini grade (n = 16, 28.1%) at Month 18, when compared to baseline. Among 30 evaluable patients with Perugini grade ≥2 at baseline who were treated with vutrisiran, the Perugini grade was reduced by ≥1 in 15 (50.0%) patients and remained unchanged in 15 (50.0%) patients at Month 18 (**Table 1**).[1]

Table 1. Change from Baseline in Perugini Grade at Month 18.[1a]

Perugini Grade at Baseline	Perugini Grade at Month 18, n (%)			
	0	I	II	III
0	24 (42.1)	1 (1.8)	0	0
I	1 (1.8)	0	1 (1.8)	0
II	0	0	2 (3.5)	0
III	2 (3.5)	3 (5.3)	10 (17.5)	13 (22.8)

Abbreviations: mITT = modified intent-to-treat.
[a]Analysis includes vutrisiran-treated patients from mITT population with evaluable data at baseline and Month 18 (n=57).
Pink indicates increased Perugini grade, light gray indicates no change in Perugini grade, blue indicates reduced Perugini grade.

Safety Results

Vutrisiran demonstrated an acceptable cardiac safety profile, with the majority of AEs being mild or moderate in severity during the 18-month treatment period.[1,2]

There were no drug-related discontinuations or deaths. Three patients (2.5%) in the vutrisiran arm discontinued the study due to AEs (2 due to death, 1 due to a non-fatal heart failure event), none of which were considered related to vutrisiran. One death was due to COVID-19 pneumonia, and the other was due

to iliac artery occlusion. Two SAEs (dyslipidemia and urinary tract infection) were deemed related to vutrisiran by the Investigators.[2]

AEs occurring in ≥10% of patients in the vutrisiran arm included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness; all of these AEs, with the exception of arthralgia and pain in extremity, were reported at a similar or lower frequency than in the external placebo arm. ISRs were reported in 5 patients (4.1%) receiving vutrisiran, all of which were mild and transient. Overall, there were no safety signals regarding liver function tests, hematology, or renal function related to vutrisiran.[2]

A cardiac safety summary of HELIOS-A at 18 months is presented in **Table 2**.[1]

Table 2. HELIOS-A 18-Month Cardiac Safety Summary.[1]

Variable, n (%)	APOLLO mITT	HELIOS-A mITT	APOLLO Cardiac Subpopulation	HELIOS-A Cardiac Subpopulation
	Placebo (N=77)	Vutrisiran (N=122)	Placebo (N=36)	Vutrisiran (N=40)
Cardiac AEs[a]	28 (36.4)	37 (30.3)	13 (36.1)	15 (37.5)
Cardiac SAEs[a]	10 (13.0)	11 (9.0)	4 (11.1)	6 (15.0)
Cardiac arrhythmia AEs	22 (28.6)	30 (24.6)	11 (30.6)	13 (32.5)
Supraventricular arrhythmias	13 (16.9)	10 (8.2)	9 (25.0)	7 (17.5)
Cardiac conduction disorders	7 (9.1)	10 (8.2)	3 (8.3)	4 (10.0)
Ventricular arrhythmias and cardiac arrest	6 (7.8)	6 (4.9)	3 (8.3)	1 (2.5)
Rate and rhythm disorders	0	8 (6.6)	0	3 (7.5)
Cardiac failure AEs	8 (10.4)	7 (5.7)	2 (5.6)	5 (12.5)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified intent-to-treat; SAE = serious adverse event.
[a]Based on MedDRA 'Cardiac Disorders' System Organ Class.

CASE REPORTS

The following information provides an overview of a published case report regarding the use of technetium scintigraphy in a patient treated with vutrisiran. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Smiley DA, et al. Gene silencing therapy in hereditary (variant) transthyretin cardiac amyloidosis: A puzzling case of decreasing pyrophosphate uptake on scintigraphy. *Circ Cardiovasc Imaging.* 2023;16(8). doi:10.1161/CIRCIMAGING.123.015243[3]

- A case report detailed a 46-year-old male patient diagnosed with hATTR with the Glu89Gln variant. Due to family history, the patient underwent genetic testing at 30 years old and was asymptomatic at the time.
- At 37 years old, the patient developed symptoms including cramps in the lower extremities, numbness in the feet, and bilateral hand stiffness. At 39 years old, the patient underwent neurological evaluation as well as cardiac testing. A ^{99m}Tc-PYP scan was performed and demonstrated diffuse myocardial uptake, with a Perugini grade of 3 and a H/CL ratio of 1.56. The patient did not have any cardiac symptoms at the time.
- The patient was initiated on oral diflunisal 250 mg daily for 4 months. He was subsequently enrolled in the HELIOS-A trial and was transitioned to subcutaneous vutrisiran 25 mg every 3 months. After

17 months of treatment (4 months of diflunisal followed by 13 months of vutrisiran), the patient underwent another ^{99m}Tc-PYP scan, which showed Perugini grade 1 uptake.

ABBREVIATIONS

^{99m}Tc = ^{99m}technetium; ^{99m}Tc-DPD = ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP = ^{99m}technetium-hydroxymethylene diphosphonate; ^{99m}Tc-PYP = ^{99m}technetium-pyrophosphate; AE = adverse event; hATTR = hereditary transthyretin amyloidosis; H/CL = heart to contralateral lung; ISR = injection site reaction; IV = intravenous; LV = left ventricle; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified intent-to-treat; mNIS+7 = modified neuropathy impairment score +7; SAE = serious adverse event; Tc = technetium.

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REFERENCES

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2. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26. doi:10.1080/13506129.2022.2091985
3. Smiley DA, Einstein AJ, Mintz A, et al. Gene silencing therapy in hereditary (variant) transthyretin cardiac amyloidosis: A puzzling case of decreasing pyrophosphate uptake on scintigraphy. *Circ Cardiovasc Imaging*. 2023;16(8):e015243. doi:10.1161/CIRCIMAGING.123.015243