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, the majority of cardiac AEs in the vutrisiran group were mild or moderate in severity.[1,2]

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; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; COPD = chronic obstructive pulmonary disease; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; H/CL = heart to contralateral lung; HFpEF = heart failure with preserved ejection fraction; H/L = heart to 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; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; RNAi = ribonucleic acid interference; SAE = serious adverse event; SPECT/CT = single-photon emission computed tomography/computed tomography; Tc = technetium.

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CLINICAL DATA

HELIOS-A

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. 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

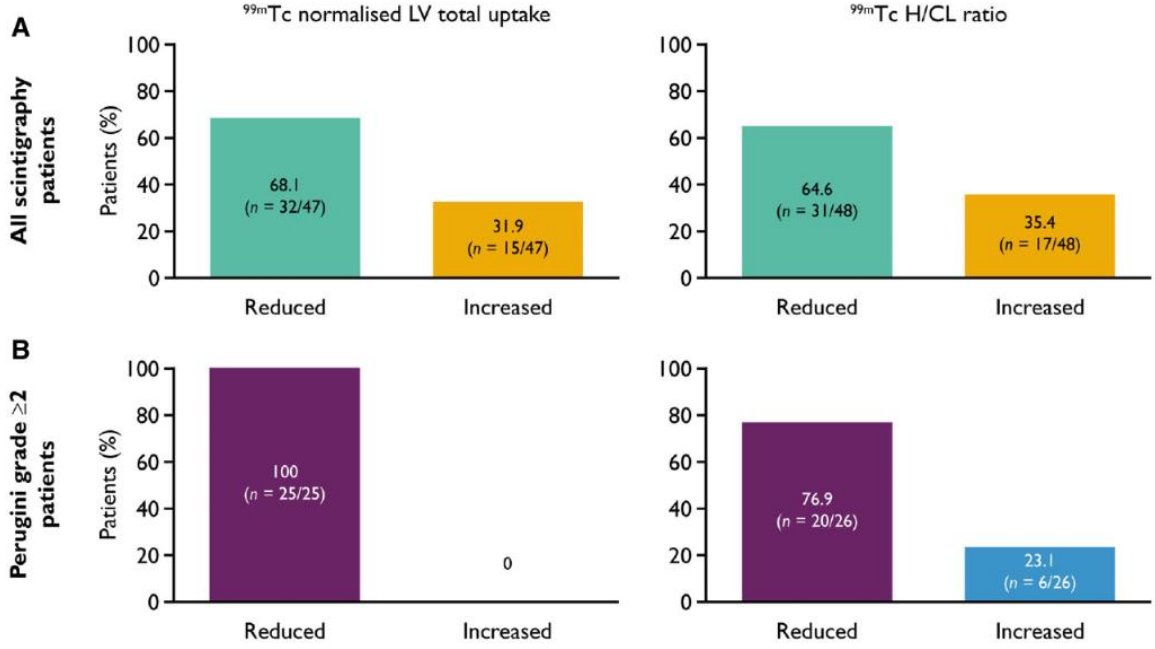
APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[2]

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.
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.[1,a]

Perugini Grade at Baseline	Perugini Grade at Month 18, n (%)			
	0	**1**	**2**	**3**
0	24 (42.1)	1 (1.8)	0	0
1	1 (1.8)	0	1 (1.8)	0
2	0	0	2 (3.5)	0
3	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).

Perugini grade is a 0-3 scale, where 0 represents no cardiac uptake of the radiotracer and normal bone uptake, 1 represents cardiac uptake that is less than bone uptake, 2 represents cardiac uptake with a similar intensity to bone uptake, and 3 represents cardiac uptake with attenuated or absent bone uptake.

Pink indicates increased Perugini grade (n=2), light gray indicates no change in Perugini grade (n=39), blue indicates reduced Perugini grade (n=16).

Safety Results

During the 18-month treatment period of HELIOS-A, the majority of AEs and cardiac AEs in the vutrisiran group were mild or moderate in severity.[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 concerns 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 published case reports regarding the use of technetium scintigraphy in patients treated with vutrisiran. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Almanzar A, Rahman A, Hamed M, et al. Val142Ile ATTR Cardiomyopathy: From Disease Progression to Clinical Stabilization With Vutrisiran. *JACC Case Rep*. 2026;31(35):109237. doi:10.1016/j.jaccas.2026.109237[3]

- An 83-year-old African American female with a past medical history of atrial fibrillation, HFpEF, COPD, obstructive sleep apnea, hypertension, prediabetes, and coronary artery calcification presented to a heart failure clinic with progressive exertional dyspnea. ATTR-CM was suspected and the patient received transthoracic echocardiography and ^{99m}Tc-PYP SPECT imaging. Genetic testing confirmed hATTR diagnosis with variant TTR c.424G >A (p.Val142Ile).
- The patient was treated with tafamidis and guideline directed medical therapy for management of heart failure. The patient experienced a progression of worsening cardiac symptoms and mild neurologic symptoms. The patient was then started on vutrisiran, which resulted in symptom stabilization, improved NT-proBNP, and stable neurological status.

Malik MR, Dalia T, Shah Z. A mutation in transthyretin gene in a Mexican patient leading to hereditary amyloidosis: a case report. *J Med Case Rep*. 2025;19(1):384. doi:10.1186/s13256-025-05308-w[4]

- A 66-year-old Mexican male presented with chest pain and shortness of breath. He also had urinary incontinence, back pain, and neuropathic symptoms in his feet. His past medical history included spontaneous biceps tendon rupture, rotator cuff tear, and bilateral carpal tunnel syndrome. A cardiac amyloidosis diagnosis was suspected and the patient received a ^{99m}Tc-PYP scan with a H/CL

ratio of 2.07 and grade 3 myocardial radiotracer uptake. Genetic testing showed the patient was heterozygous for p.G67A confirming a diagnosis of hATTR.

- The patient was treated with tafamidis and vutrisiran. At 1-year follow-up, he experienced improvement in neuropathic symptoms. A repeat ^{99m}Tc-PYP scan showed a visual grade 3 and H/CL ratio of 1.69.

Hung YH, Yu AL, Chen YC, et al. Use of technetium-99m-pyrophosphate single-photon emission computed tomography/computed tomography in monitoring therapeutic changes of RNA interference therapeutics in patients with hereditary transthyretin amyloid cardiomyopathy. *J Formos Med Assoc*. 2025;124(4):333-339. doi:10.1016/j.jfma.2024.10.005[5]

- A retrospective analysis of 8 patients enrolled in the phase 3 APOLLO and HELIOS-A studies at National Taiwan University Hospital was conducted to assess changes in ^{99m}Tc-PYP SPECT/CT imaging results in patients receiving patisiran (n=6) or vutrisiran (n=2) based on first and second image follow-up.
- Additional information on the treatment outcomes, including the change in visual score, planar H/CL ratio, and volumetric H/L ratio, by both cohorts and in the overall group are provided in the publication.

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[6]

- 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 of age and was asymptomatic at the time.
- At 37 years of age, the patient developed symptoms including cramps in the lower extremities, numbness in the feet, and bilateral hand stiffness. At 39 years of age, 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.

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