Baseline Characteristics of Patients with Transthyretin Cardiac Amyloidosis Enrolled in the Patisiran Expanded Access Program

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Introduction

ATTR Amyloidosis

- ATTR amyloidosis is a progressive, multisystem, and fatal disease[1,2]
- Ongoing TTR amyloid deposition in the heart drives the progression of CM, leading to:[1–3]
  - Worsening heart failure and arrhythmias
  - A decline in functional status, quality of life, and death[3–6]
- Treatment for patients with ATTR cardiac amyloidosis is limited; tafamidis (a TTR stabilizer) is currently the only FDA-approved treatment for CM of ATTR amyloidosis in the USA[7,8]

Patisiran

- IV-administered RNAi therapeutic approved for hereditary or ATTRv amyloidosis with polyneuropathy[9–11]
- Prior clinical data in patients with ATTRv amyloidosis with polyneuropathy suggest the potential for patisiran to improve cardiac manifestations of ATTR amyloidosis[12,13]

Patisiran ATTR-CM EAP

- After positive results from the Phase 3 APOLLO-B study (NCT03997383), in which patisiran preserved functional capacity, health status, and quality of life in patients with ATTR amyloidosis with CM compared with placebo,[14] an EAP was established and is ongoing in the USA to provide patisiran for patients who have clinically worsening disease despite tafamidis or other disease-directed therapy

Objective

- To report the demographics, baseline characteristics, and safety data for patients enrolled in the patisiran ATTR-CM EAP

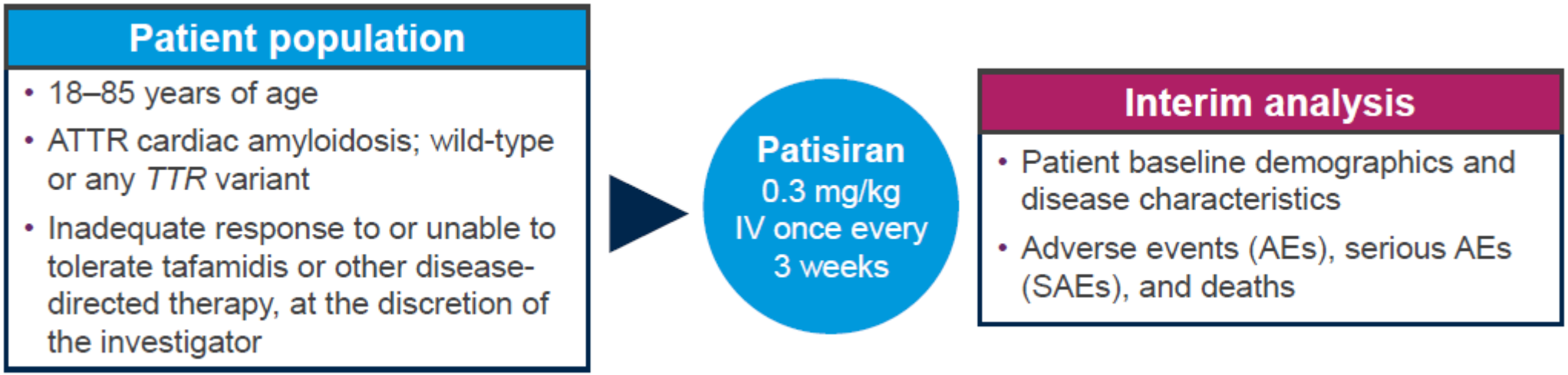
ATTR, transthyretin-mediated; ATTRv, hereditary or variant transthyretin-mediated; CM, cardiomyopathy; EAP, expanded access program; FDA, Food and Drug Administration; IV, intravenous; RNAi, RNA interference; TTR, transthyretin. 1. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–91; 3. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 4. Fontana et al. *Circulation* 2015;132:1570–9; 5. Lane et al. *Circulation* 2019;140:16–26; 6. Nativi-Nicolau et al. *ESC Heart Failure* 2021;8:3875–84; 7. Ioannou et al. *Eur Heart J* 2023;ehad347; 8. Rahman et al. *Oxford Medical Case Reports* 2021;8:283–7; 9. Coelho et al. *N Engl J Med* 2013;369:819–29; 10. Alnylam Pharmaceutics Inc. 2023. https://www.alnylam.com/sites/default/files/pdfs/ONPATTRO-Prescribing-Information.pdf; 11. European Medicines Agency 2018. https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf; 12. Solomon et al. *Circulation* 2019;139:431–43; 13. Adams et al. *N Engl J Med* 2018;379:11–21; 14. Maurer et al. *HFSA Congress 2022*. Poster Presentation.

Methods

Design

- The patisiran ATTR-CM EAP is an open-label, multicenter, single-arm program (**Figure 1**)
- All analyses reported are descriptive

Figure 1. Design



AE, adverse event; ATTR, transthyretin-mediated; CM, cardiomyopathy; EAP, expanded access program; IV, intravenous; SAE, serious adverse event; TTR, transthyretin.

Patient Disposition and Baseline Characteristics

Patient disposition

- At the cut-off, 22 sites had been activated with 20 sites recruiting
- A total of 200 patients were enrolled, of whom 183 (91.5%) were ongoing at cut-off

Baseline characteristics

- At diagnosis, almost all patients were ≥60 years of age, with approximately half over 75 years of age, and the mean age was 73.8 years (**Table 1**)
- Most patients were male (94.5%) and white (90.9%)
- The majority of patients had ATTRwt cardiac amyloidosis and Stage 1 disease (**Table 1**)
  - V122I was the most common mutation (n=10); other reported mutations were 1 each for T60A, D18N, and T60I
- Approximately two-thirds of patients were diagnosed within a year of symptom onset; 26.5% experienced a diagnostic delay of 1–10 years (**Table 2**)

ATTRwt, wild-type transthyretin-mediated.

Patient Disposition and Baseline Characteristics (cont'd)

Table 1. Baseline Characteristics

Characteristic	Patisiran (n=200)
Mean age at diagnosis, years	73.8
Age at diagnosis, %	
<60 years	2.0
60–75 years	49.5
>75 years	48.5
Mean age at enrollment, years	75.4
Male, %	94.5
White, %	90.9
Genotype, %	
ATTRwt	93.5
ATTRv	6.5
National Amyloidosis Centre ATTR Stage,[a] %	
1	64.5
2	26.0
3	9.5

Table 2. Time to Diagnosis

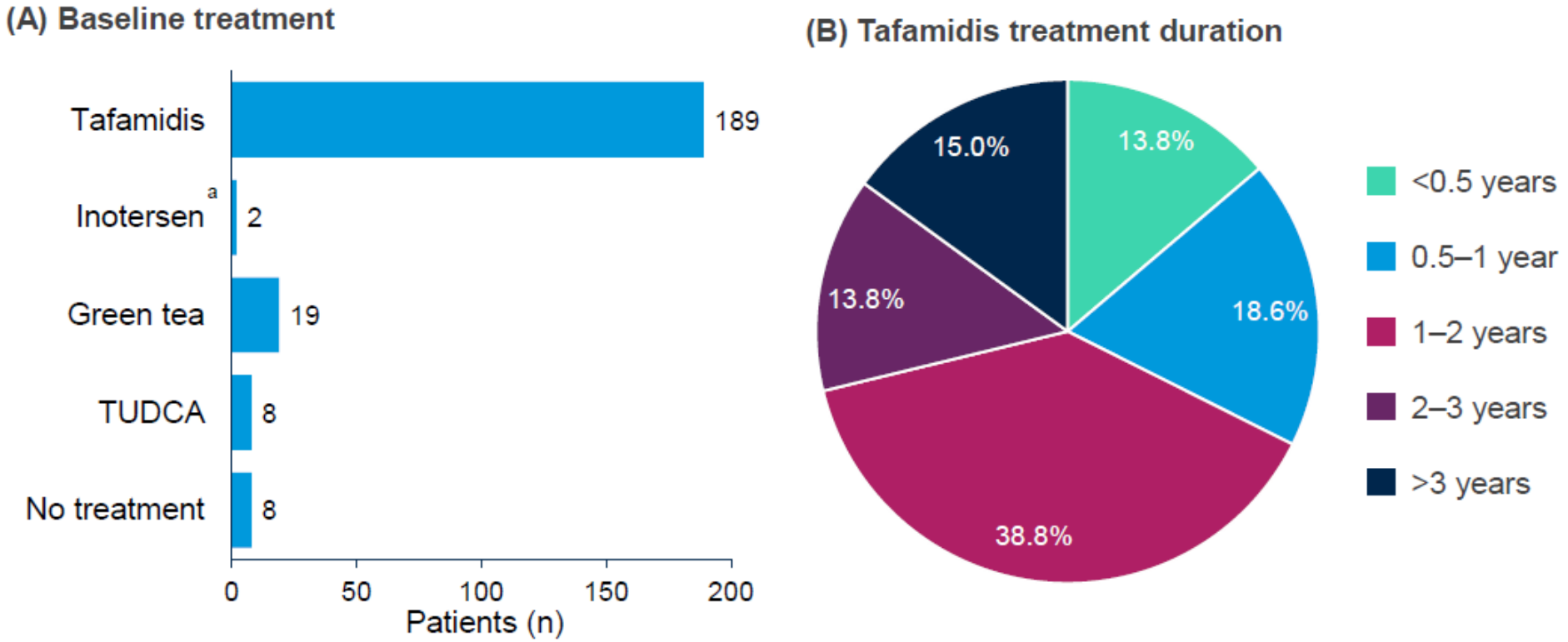
	Patisiran (n=200)
Time from symptom onset to diagnosis, %	
≤1 year	69.0
>1–10 years	26.5
>10 years	4.5
Years to diagnosis, n	
<1 year	102
1 year	36
2 years	24
3 years	5
4 years	5

[a]Stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min/1.73 m^2; Stage 2 (intermediate risk): all patients not meeting criteria for Stage 1 or 3; Stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m^2.[15] ATTR, transthyretin-mediated; ATTRv, hereditary or variant transthyretin-mediated; ATTRwt, wild-type transthyretin-mediated; eGFR, estimated glomerular filtration rate; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide. 15. Gillmore et al. *Eur Heart J* 2018;39:2799–806.

Treatment at baseline

- Tafamidis was the most common treatment at baseline (**Figure 2A**)
  - Other treatments included green tea and TUDCA
- Tafamidis treatment duration ranged from <0.5 years to >3 years, with most patients receiving it for up to 2 years (**Figure 2B**)

Figure 2. Baseline Treatment

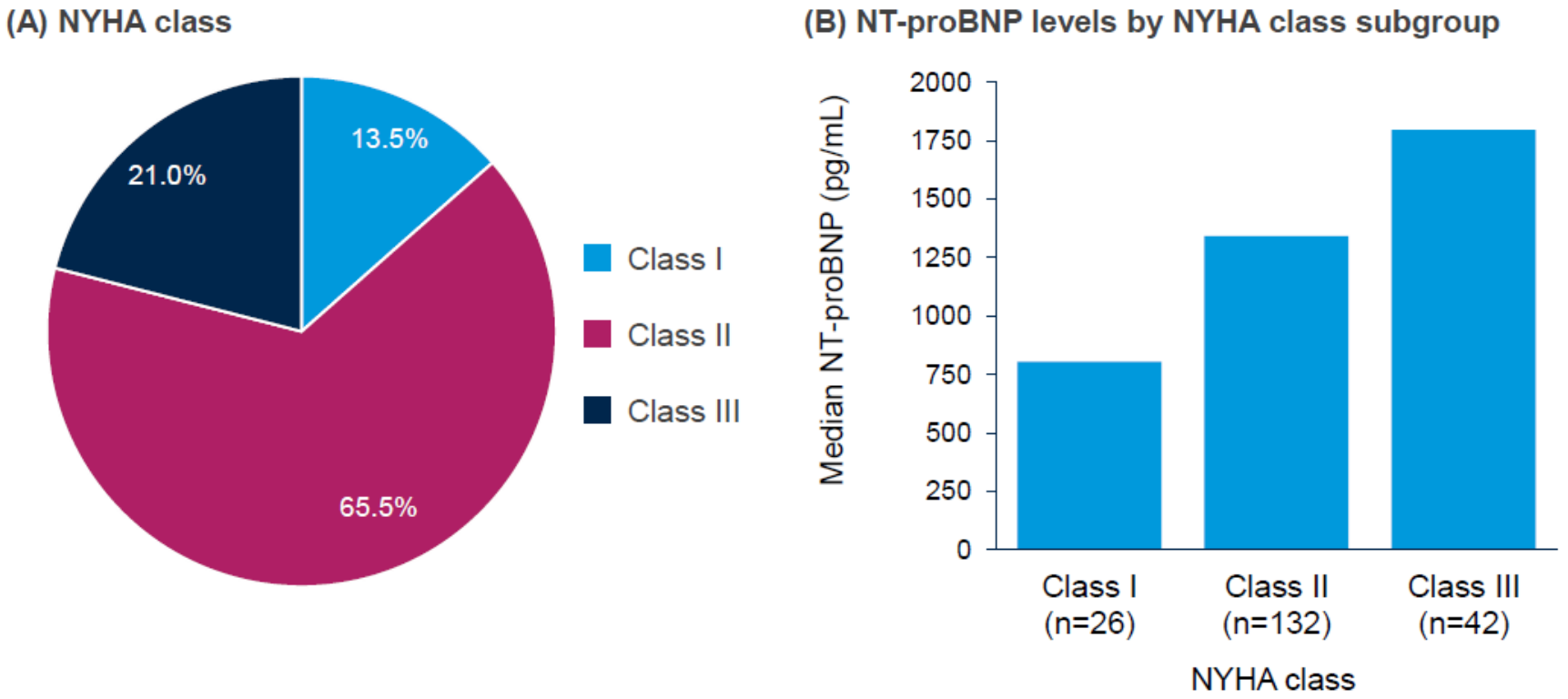


[a]Patients receiving inotersen discontinued prior to enrollment in the patisiran ATTR-CM EAP. ATTR, transthyretin-mediated; CM, cardiomyopathy; EAP, expanded access program; TUDCA, tauroursodeoxycholic acid.

NYHA class

- Overall, 13.5% of patients were in NYHA Class I, 65.5% were in Class II, and 21.0% were in Class III (**Figure 3A**)
- NT-proBNP levels correlated with NYHA class, with the highest levels seen in patients in NYHA Class III (**Figure 3B**)

Figure 3. NYHA Class

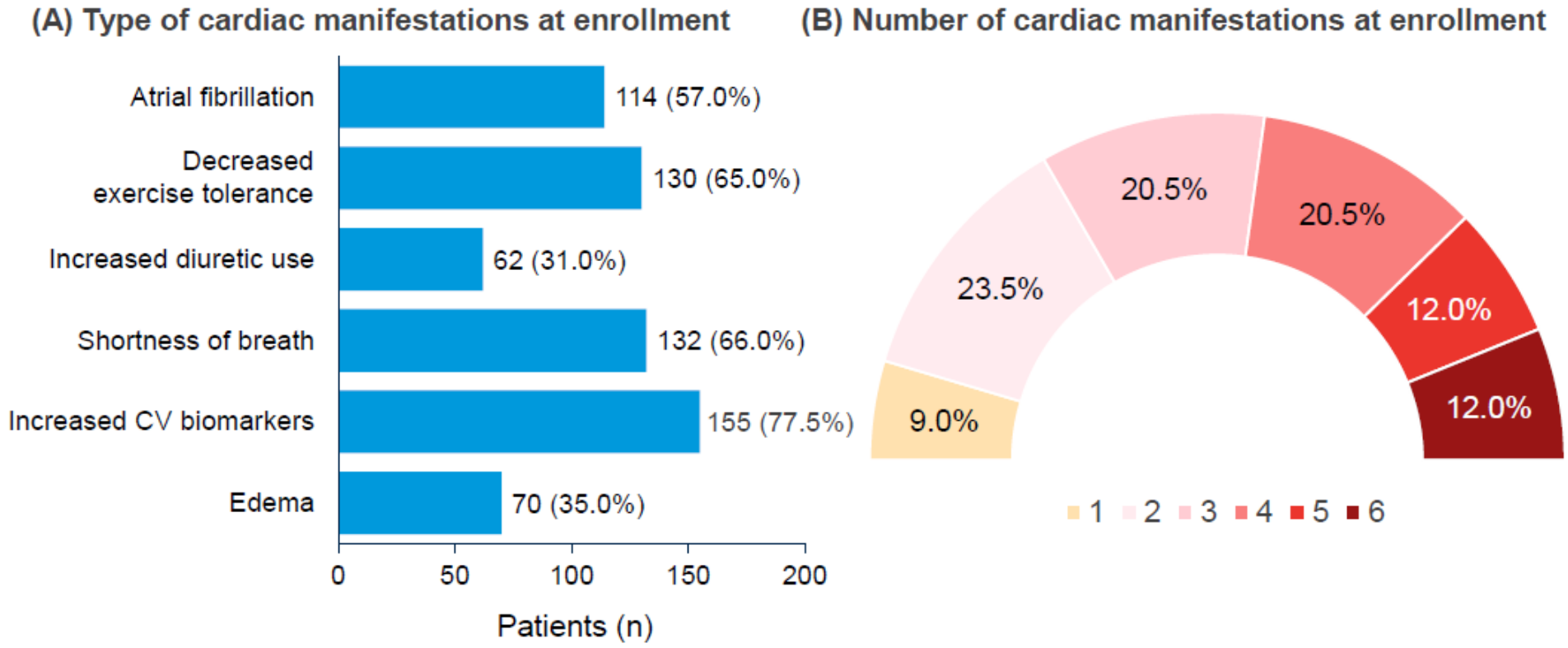


NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association.

Cardiac Manifestations

- The most frequently reported markers of progression leading to patisiran ATTR-CM EAP enrollment were increased CV biomarkers (77.5%) (**Figure 4A**)
  - 88.5% of patients had progressed in >1 cardiac manifestation despite treatment, and 44.5% had progressed in ≥4 manifestations (**Figure 4B**)

Figure 4. Cardiac Manifestations Progressed Under Prior Treatment



ATTR, transthyretin-mediated; CM, cardiomyopathy; CV, cardiovascular; EAP, expanded access program.

Kidney Function

- Most patients had eGFR levels between 45 and 90 mL/min/1.73 m^2 (**Table 3**)

Table 3. Kidney Function[a]

eGFR level, mL/min/1.73 m^2, n (%)	Patisiran (n=200)
<45	35 (17.5)
≥45–<60	70 (35.0)
≥60–<90	82 (41.0)
≥90	13 (6.5)

[a]Protocol exclusion: NYHA Class III and ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m^2).[15] eGFR, estimated glomerular filtration rate; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association. 15. Gillmore et al. *Eur Heart J* 2018;39:2799–806.

Safety

- The most common AEs were IRRs (back pain [18%] and chest pain/discomfort [4.5%]), insomnia, fatigue, dyspnea, and COVID-19 infection (**Table 4**)
  - Nine patients discontinued due to an IRR, five due to death, and one each due to declining health, withdrawn consent, and heart transplant

Table 4. Safety

Event, n (%)	Patisiran (n=200)
Any AE	189 (94.5)
SAE	44 (22.0)
AE leading to study drug discontinuation	17 (8.5)
Cardiac AE	19 (9.5)
Cardiac SAE	14 (7.0)
Death	5 (2.5)
Most common AEs	
IRR	73 (36.5)
Insomnia	7 (3.5)
Dyspnea	6 (3.0)
Fatigue	6 (3.0)
COVID-19 infection	5 (2.5)

NOTE: Data from Trial Safety Database. Safety data cut-off June 30, 2023. AE, adverse event; IRR, infusion-related reaction; SAE, serious AE.

Conclusions

- Patients with ATTR cardiac amyloidosis enrolled in the patisiran CM EAP had a significant symptom burden at baseline despite receiving treatment with tafamidis or other disease-directed therapy
- At enrollment in the EAP, nearly all patients continued treatment with tafamidis or other disease-directed therapy
- Among patients in the EAP, the safety profile of patisiran was acceptable; patisiran is an investigational therapy in development for the treatment of the CM of ATTR amyloidosis

ATTR, transthyretin-mediated; CM, cardiomyopathy; EAP, expanded access program.

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