Patisiran: Use in Patients with Renal Impairment

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SUMMARY

- No dose adjustment of patisiran is necessary in patients with mild or moderate renal impairment (eGFR ≥30 to <90 mL/min/1.73m^2). Patisiran has not been studied in patients with severe renal impairment or ESRD.[1]
- A post-hoc analysis of data from patisiran clinical trials was conducted to assess the efficacy and safety of patisiran in patients with ATTR and comorbid CKD. Patients were stratified by baseline eGFR (<60 mL/min/1.73m^2 or ≥60 mL/min/1.73m^2).[2]
  - During patisiran treatment, mean eGFR remained stable, regardless of baseline kidney function.
  - No new safety signals were observed during patisiran treatment in patients with a baseline eGFR <60 mL/min/1.73m^2.
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns with the use of patisiran in patients with a history of severe renal impairment or ESRD.[3]

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POST-HOC ANALYSIS IN PATIENTS WITH ATTR AND CKD

A post-hoc analysis was conducted to evaluate the efficacy and safety of patisiran in patients with ATTR with and without comorbid mild to moderate CKD. Data were used from the following patisiran clinical trials[2]:

- The Phase 3 APOLLO study, a randomized, double-blind, placebo-controlled study in patients with hATTR-PN[4]
- The Phase 3 APOLLO-B study, a randomized, double-blind, placebo-controlled study in patients with ATTR-CM, including both hATTR and wtATTR[5]
- The Phase 3b, open-label study in patients with hATTR-PN who had disease progression post-OLT[6]

- The Phase 2 OLE study in patients with hATTR-PN who completed the patisiran Phase 2 study[7]
- The Global OLE study in patients with hATTR-PN who completed the Phase 2 OLE or APOLLO studies.[8]

A total of 634 patients were included in the analysis. Overall, 158 (24.9%) patients had a baseline eGFR <60 mL/min/1.73m^2. Select baseline characteristics of patients across all studies are presented in **Table 1**.[2]

Table 1. Baseline eGFR Across Patisiran Clinical Studies.[2]

hATTR-PN				
	Phase 2 OLE	**APOLLO**		**Post-OLT**
	Patisiran (n=27)	**Placebo (n=77)**	**Patisiran (n=148)**	**Patisiran (n=23)**
Median age at screening (range), year	64 (29-77)	63 (34-80)	62 (24-83)	58 (43-75)
NYHA Class, n (%)[a]				
No heart failure[b]	N/A	N/A	N/A	13 (65.5)
I	19 (70.4)	40 (52.0)	70 (47.0)	5 (21.7)
II	7 (25.9)	36 (47.0)	77 (52.0)	5 (21.7)
III	0	0	0	0
eGFR, n (%), (min-max)				
<60 mL/min/1.73m^2	1 (3.7) (58-58)	5 (6.5) (32-60)	16 (10.8) (31-60)	9 (39.1) (37-56)
≥60 mL/min/1.73m^2	26 (96.3) (62-153)	72 (93.5) (60-228)	132 (89.2) (60-346)	14 (60.9) (63-114)
ATTR-CM				
	APOLLO-B			
	hATTR		**wtATTR**	
	Placebo (n=34)	**Patisiran (n=37)**	**Placebo (n=144)**	**Patisiran (n=144)**
Median age at screening (range), year	66 (41-85)	70 (47-85)	77 (59-85)	77 (59-85)
NYHA Class, n (%)				
I	4 (11.8)	2 (5.4)	11 (7.6)	8 (5.6)
II	28 (82.4)	33 (89.2)	122 (84.7)	123 (85.4)
III	2 (5.9)	2 (5.4)	11 (7.6)	13 (9.0)
eGFR, n (%), (min-max)				
<60 mL/min/1.73m^2	8 (23.5) (23-59)	10 (27.0) (31-59)	61 (42.4) (27-59)	48 (33.3) (30-59)
≥60 mL/min/1.73m^2	26 (76.5) (61-162)	24 (64.9) (61-223)	81 (56.3) (60-162)	95 (66.0) (60-138)

Abbreviations: ATTR-CM = transthyretin amyloidosis with cardiomyopathy; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; NYHA = New York Heart Association ; OLE = open-label extension; OLT = orthotopic liver transplant; wtATTR = wild-type transthyretin amyloidosis.

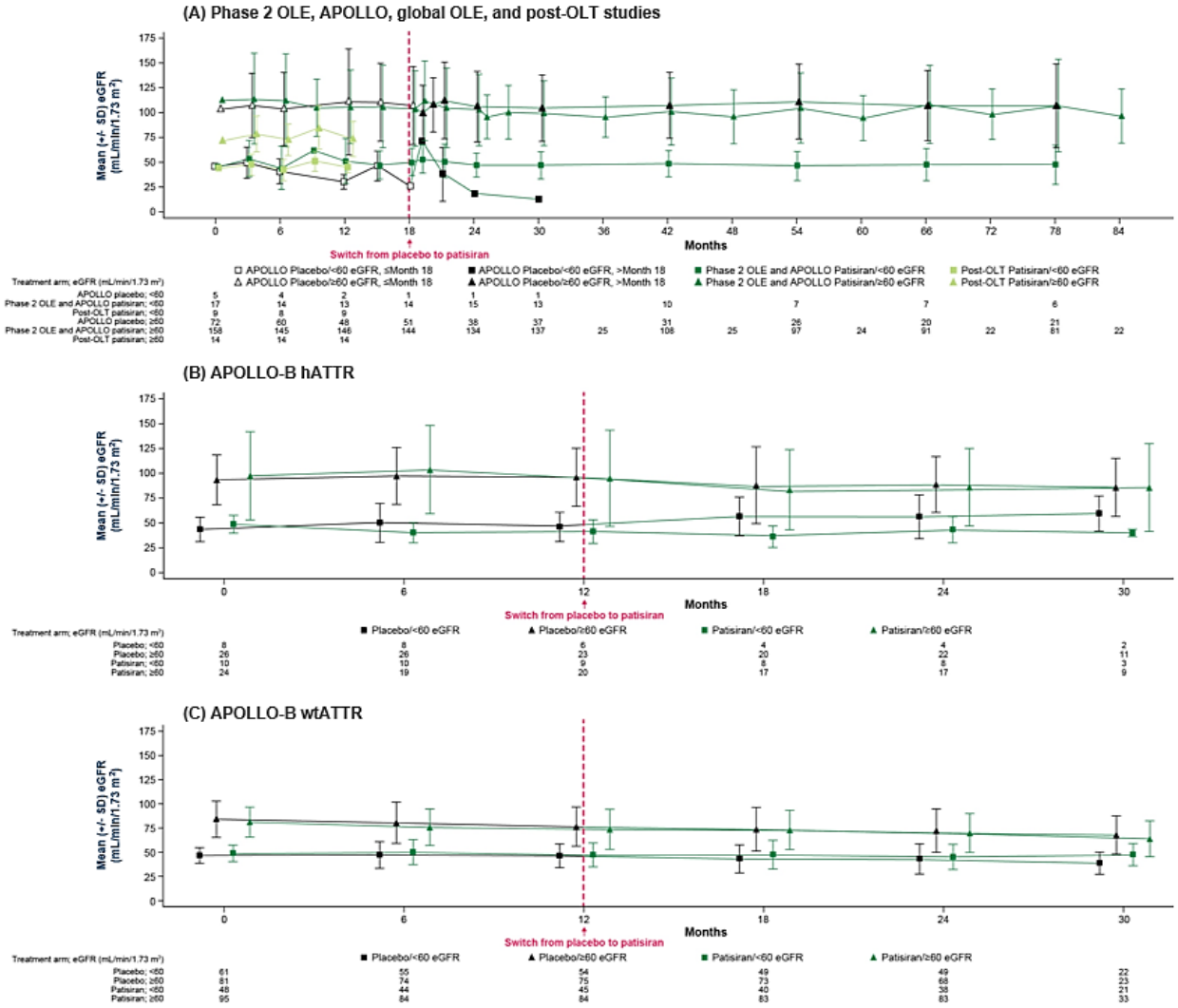
[a]Baseline NYHA class was missing in 1 patient in the Phase 2 OLE, 1 patient in the placebo arm of APOLLO, and 1 patient in the patisiran arm of APOLLO.

[b]For the Phase 2 OLE and APOLLO studies, NYHA Class I included patients with no heart failure and patients with heart failure who had no symptomology during ordinary physical activity.

Efficacy Results

During treatment with patisiran, mean eGFR remained relatively stable over time regardless of baseline kidney function (**Figure 1**).[2]

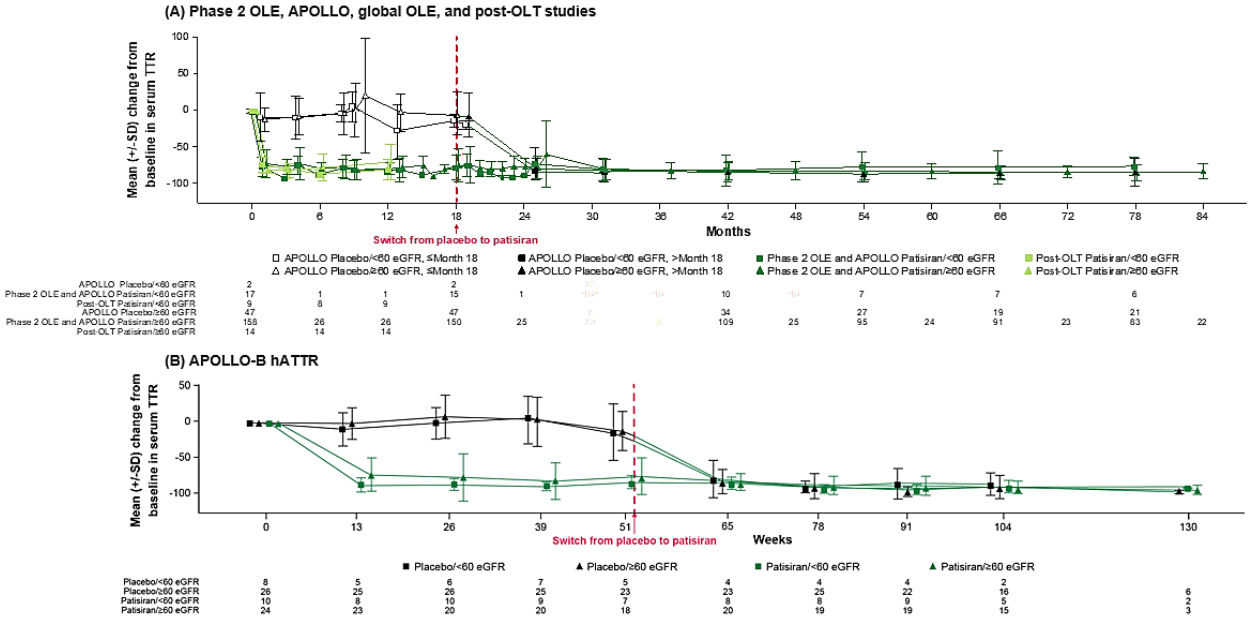
Figure 1. Change in Mean eGFR Over Time by Baseline eGFR Subgroups.[2]



Abbreviations: eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; OLE = open-label extension; OLT = orthotopic liver transplant; SD = standard deviation; wtATTR = wild-type transthyretin amyloidosis.
From Dang et al.[2]

Treatment with patisiran resulted in serum TTR knockdown that was consistent and maintained across the studies, regardless of baseline eGFR (**Figure 2**).[2]

Figure 2. Serum TTR Knockdown by Baseline eGFR.[2]



Abbreviations: eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; OLE = open-label extension; OLT = orthotopic liver transplant; SD = standard deviation; TTR = transthyretin.
From Dang et al.[2]

Safety Results

Safety with patisiran treatment was assessed in patients with baseline eGFR <60 mL/min/1.73m^2, and no new safety signals were observed. Renal and urinary AEs reported across the studies are presented in **Table 2** and **Table 3**.[2]

Table 2. Renal and Urinary AEs in Patients with hATTR-PN and Baseline eGFR <60 mL/min/1.73m².[2]

Events, n (%)	hATTR-PN			
	Phase 2 OLE/Global OLE	APOLLO/Global OLE		Post-OLT
	Patisiran (n=1) [PY=2.1]	Placebo/Patisiran [a] (n=5) [PY=6.8]	Patisiran (n=16) [PY=73.2]	Patisiran (n=9) [PY=9.8]
≥1 AE	0	2 (40.0)	7 (43.8)	0
Renal and urinary AEs	0	2 (40.0)	7 (43.8)	0
AKI	0	0	2 (12.5)	0
CKD	0	0	2 (12.5)	0
Dysuria	0	1 (20.0)	2 (12.5)	0
ESRD	0	1 (20.0)	0	0
Hematuria	0	1 (20.0)	1 (6.3)	0
Neurogenic bladder	0	0	1 (6.3)	0
Oliguria	0	0	1 (6.3)	0
Renal failure	0	0	0	0
Renal impairment	0	1 (20.0)	0	0
Urinary incontinence	0	0	1 (6.3)	0
Urinary retention	0	1 (20.0)	0	0

Abbreviations: AE = adverse event; AKI = acute kidney injury; CKD = chronic kidney disease; ESRD = end stage renal disease; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; OLE = open-label extension; OLT = orthotopic liver transplant; PY = patient year.

[a]Placebo patients switched to patisiran at 18 months after entering the Global OLE. Only events occurring on patisiran are presented.

Table 3. Renal and Urinary AEs in Patients with hATTR-CM and Baseline eGFR <60 mL/min/1.73m².[2]

Events, n (%)[a]	hATTR-CM	
	APOLLO-B hATTR	
	Placebo (n=8) [PY=7.6]	Patisiran (n=10) [PY=10.3]
≥1 AE	8 (100.0)	9 (90.0)
Renal and urinary AEs	2 (25.0)	3 (30.0)
AKI	0	0
CKD	0	0
Dysuria	0	0
ESRD	0	0
Hematuria	0	1 (10.0)
Neurogenic bladder	0	0
Oliguria	0	0
Renal failure	1 (12.5)	0
Renal impairment	1 (12.5)	1 (10.0)
Urinary incontinence	0	0
Urinary retention	0	1 (10.0)

Abbreviations: AE = adverse event; AKI = acute kidney injury; CKD = chronic kidney disease; ESRD = end stage renal disease; hATTR = hereditary transthyretin amyloidosis; hATTRCM = hereditary transthyretin amyloidosis with cardiomyopathy; PY = patient year.

[a]Events reported during the 12-month double-blind period.

POOLED SAFETY POPULATION

In a pooled safety population analysis (N=224) including data from the completed Phase 2 OLE, completed Phase 3 APOLLO, and Global OLE (as of January 27, 2021) studies, 48 (21.4%) patients had mild renal impairment, 22 (9.8%) patients had moderate renal impairment, and 1 (0.4%) patient had severe renal impairment at baseline. Patients with severe renal impairment were excluded from patisiran clinical trials. No renal safety concerns have been reported in the patisiran clinical trials. No increased risk of adverse events was associated with administration of patisiran to patients with mild or moderate renal impairment (eGFR ≥30 to <90 mL/min/1.73m^2), and no dose adjustments were necessary.[3]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns with the use of patisiran in patients with a history of severe renal impairment or ESRD. Use in patients with severe renal impairment or ESRD will continue to be closely monitored by Alnylam through routine pharmacovigilance activities.[3]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The **USE IN SPECIFIC POPULATIONS** section provides the following information[1]:

Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/min/1.73m^2). ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

The **CLINICAL PHARMACOLOGY** section provides the following information[1]:

Pharmacokinetics

Specific Populations

Age, race (non-Caucasian vs. Caucasian), sex, and prior liver transplantation had no impact on the steady state pharmacokinetics of patisiran or TTR reduction. Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR ≥30 to <90 mL/min/1.73m^2) or mild hepatic impairment (bilirubin ≤1 x ULN and AST >1 x ULN, or bilirubin >1.0 to 1.5 x ULN) on patisiran exposure or TTR reduction. ONPATTRO has not been studied in patients with severe renal impairment, end-stage renal disease, or moderate or severe hepatic impairment.

ABBREVIATIONS

AE = adverse event; AKI = acute kidney injury; AST = aspartate transaminase; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; hATTR = hereditary transthyretin amyloidosis; hATTR-CM = hereditary transthyretin amyloidosis with cardiomyopathy; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; OLE = open-label extension; OLT = orthotopic liver transplant; PY = patient-year; TTR = transthyretin; ULN = upper limit of normal; wtATTR = wild-type transthyretin amyloidosis.

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