Vutrisiran: Use in Patients with Renal Impairment

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SUMMARY

- Clinical pharmacology studies have demonstrated that renal excretion is a minor route of elimination for vutrisiran.[1]
- Severe renal impairment or ESRD is not anticipated to significantly influence the overall systemic exposure, liver uptake, pharmacodynamics, or safety of vutrisiran.[2]
- Patients with a baseline eGFR <30 mL/min/1.73 m^2 were excluded from the phase 3 HELIOS-A and HELIOS-B trials.[3,4]
- A post-hoc analysis of the HELIOS-B study was conducted to assess the efficacy and safety of vutrisiran in patients who advanced to CKD Stage 4 during the double-blind period.[5]
  - Among 63 patients who advanced to CKD Stage 4 or greater, treatment with vutrisiran compared with placebo resulted in a HR of 0.47 (95% CI 0.26, 0.85) in the composite of all-cause mortality and recurrent CV events in the overall population and a HR of 0.53 (95% CI 0.25, 1.13) in the monotherapy population.[5]
  - The safety profile of vutrisiran in patients with impaired renal function was consistent with the established profile observed in the overall population during the HELIOS-B study.[5,6]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns with the use of vutrisiran in patients with a history of severe renal impairment or ESRD. The available data from the global safety database do not suggest an increased risk or varying safety profile with the use of vutrisiran in this population.[2,7]

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CLINICAL DATA

Clinical Pharmacology

Vutrisiran clinical pharmacology studies conducted in both healthy subjects and patients with hATTR-PN showed the mean serum $t_{1/2}$ ranged from 4 to 7.5 hours following subcutaneous

administration After reaching the C_{max}, vutrisiran concentration declined rapidly to the LLOQ by 24 to 48 hours. Renal clearance is not a major route of elimination of vutrisiran.[1,8]

Pooled Safety Population

In a pooled PK/PD population (n=202) including data from the Phase 1 and HELIOS-A studies, patients with mild to moderate renal impairment showed similar TTR reductions to those with no renal impairment. No significant impact of impaired renal function was observed, with a less than 25% increase in C_{max} and AUC_{0-24} predicted in patients with mild or moderate renal impairment compared with patients with normal renal function.[8]

HELIOS-B Study

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind treatment period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an OLE.[6]

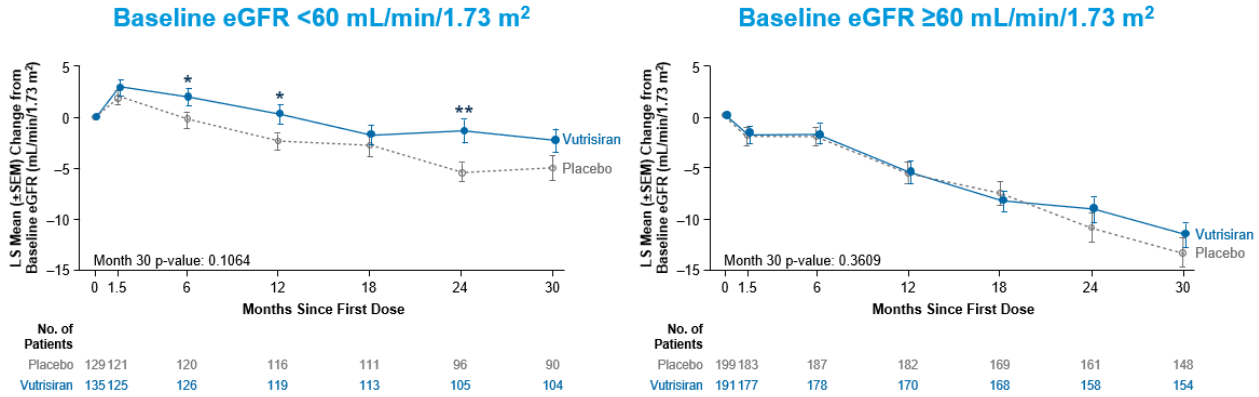
Select Exclusion Criteria

Per the HELIOS-B study protocol, patients with an eGFR <30 mL/min/1.73 m^2 (using the MDRD formula) were excluded from the study.[4]

Post-Hoc Analysis of all HELIOS-B Patients

The change from baseline in eGFR over time was evaluated in the overall population of the HELIOS-B study by patients with a baseline eGFR <60 mL/min/1.73m^2 and ≥60 mL/min/1.73m^2 (**Figure 1**).[5]

Figure 1. Change from Baseline in eGFR Over 30 Months in HELIOS-B.[5]



Abbreviations: eGFR = estimated glomerular filtration rate; LS = least squares; SEM = standard error of the mean.
*nominal p≤0.05; **nominal p≤0.01.
From Sheikh et al.[5]

Post-Hoc Analysis of Patients Advancing to CKD Stage 4 or Greater During the Double-Blind Period

Patient Demographics and Baseline Characteristics

A total of 63 patients advanced to CKD Stage 4 or greater during the double-blind period. The baseline characteristics of these patients across treatment groups are summarized in **Table 1**.[5]

Table 1. Baseline Characteristics of Patients Advancing to CKD Stage 4 or Greater.[5]

Characteristic	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo (n=32)	Vutrisiran (n=31)	Placebo (n=19)	Vutrisiran (n=18)	Placebo (n=13)	Vutrisiran (n=13)
Age, years, mean (SD)	76.4 (6.4)	76.3 (6.4)	76.1 (7.0)	76.7 (6.9)	76.8 (5.6)	75.8 (5.9)
Male, %	96.9	87.1	94.7	83.3	100.0	92.3
BMI, kg/m^2, mean (SD)	28.14 (3.58)	27.66 (3.78)	27.89 (3.66)	26.92 (3.71)	28.52 (3.56)	28.67 (3.79)
eGFR, mL/min/1.73m^2, mean (SD)	48.4 (10.0)	46.0 (13.3)	47.8 (10.2)	44.6 (13.7)	49.2 (10.2)	48.0 (13.1)
ATTR disease type, n (%)						
hATTR	2 (6.3)	8 (25.8)	0	6 (33.3)	2 (15.4)	2 (15.4)
wtATTR	30 (93.8)	23 (74.2)	19 (100)	12 (66.7)	11 (84.6)	11 (84.6)

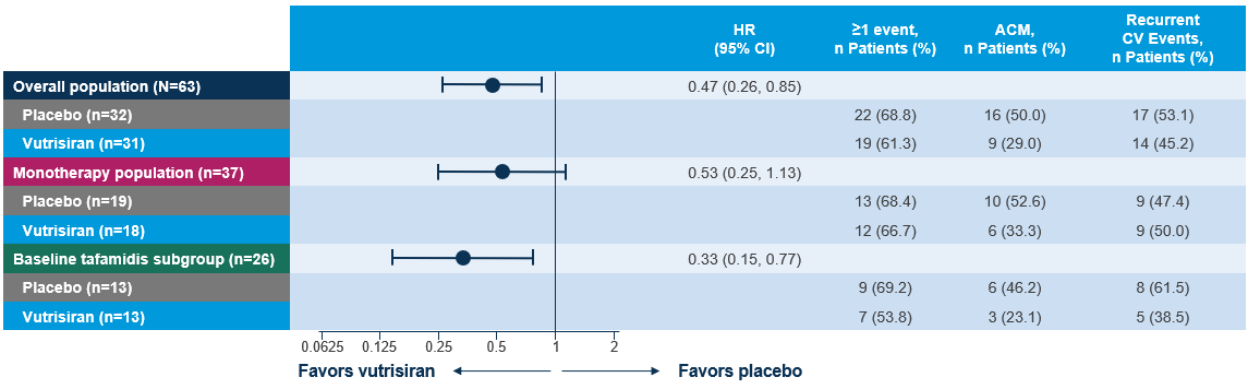
Abbreviations: ATTR = transthyretin amyloidosis; BMI = body mass index; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; SD = standard deviation; wtATTR = wild-type transthyretin amyloidosis.

Efficacy Results

In the HELIOS-B study, treatment with vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events in both the overall population (HR 0.72; 95% CI 0.56, 0.93; P=0.01) and monotherapy population (HR 0.67, 95% CI 0.49, 0.93; P=0.02).[6]

Among patients who advanced to CKD Stage 4 or greater, treatment with vutrisiran compared with placebo resulted in a HR of 0.47 (95% CI 0.26, 0.85) in the composite of all-cause mortality and recurrent CV events in the overall population and a HR of 0.53 (95% CI 0.25, 1.13) in the monotherapy population (**Figure 2**).[5]

Figure 2. Composite of All-Cause Mortality and Recurrent CV Events Among Patients Who Advanced to CKD Stage 4 or Greater.[5,a]



Abbreviations: ACM = all-cause mortality; CKD = chronic kidney disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio.
[a]Includes events occurring on or after advancement to CKD Stage ≥4.
From Sheikh et al.[5]

Safety Results

A summary of the safety results including events occurring on or after advancement to CKD Stage 4 or greater is presented in **Table 2**. The safety profile of vutrisiran in patients with impaired renal function was consistent with the established profile observed in the overall population during the HELIOS-B study.[5,6]

Table 2. Safety Results in Patients Who Advanced to CKD Stage 4 During the Double-Blind Period.[5]

Event, n (%)	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo (n=32)	Vutrisiran (n=31)	Placebo (n=19)	Vutrisiran (n=18)	Placebo (n=13)	Vutrisiran (n=13)
≥1 AE	29 (90.6)	28 (90.3)	17 (89.5)	17 (94.4)	12 (92.3)	11 (84.6)
Related to study drug	1 (3.1)	2 (6.5)	0	1 (5.6)	1 (7.7)	1 (7.7)
≥1 SAE	23 (71.9)	22 (71.0)	13 (68.4)	13 (72.2)	10 (76.9)	9 (69.2)
Related to study drug	0	0	0	0	0	0
≥1 severe AE	20 (62.5)	19 (61.3)	13 (68.4)	12 (66.7)	7 (53.8)	7 (53.8)
Related to study drug	0	0	0	0	0	0
≥1 AE leading to study drug discontinuation	1 (3.1)	0	1 (5.3)	0	0	0
Related to study drug	0	0	0	0	0	0
Death	14 (43.8)	9 (29.0)	8 (42.1)	6 (33.3)	6 (46.2)	3 (23.1)

Abbreviations: AE = adverse event; SAE = serious adverse event.

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns with the use of vutrisiran in patients with a history of severe renal impairment or ESRD. The available data from the global safety database do not suggest an increased risk or varying safety profile with use of vutrisiran in this population.[2,7]

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The **USE IN SPECIFIC POPULATIONS** section provides the following information[9]:

Renal Impairment

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

The **CLINICAL PHARMACOLOGY** section provides the following information[9]:

Pharmacokinetics: Specific Populations

No clinically significant differences in the pharmacokinetics of vutrisiran were observed based on age, sex, race, mild and moderate renal impairment (eGFR≥30 to <90 mL/min/1.73 m^2), or mild (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) and moderate (total bilirubin >1.5 to 3 × ULN and any AST) hepatic impairment. Vutrisiran has not been studied in patients with severe renal impairment, end-stage renal disease, severe hepatic impairment, or in patients with prior liver transplant.

ABBREVIATIONS

ACM = all-cause mortality; AE = adverse event; AST = aspartate aminotransferase; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; AUC_{0-24} = area under the concentration time curve from 0 to 24 hours; BMI = body mass index; C_{max} = maximum serum concentration; CKD = chronic kidney disease; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; hATTR = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HR = hazard ratio; LLOQ = lower limit of quantification; MDRD = Modification of Diet in Renal Disease; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TTR = transthyretin; ULN = upper limit of normal; wtATTR = wild-type transthyretin-mediated amyloidosis.

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