

## Supplementary Information

### *Clinical Pharmacokinetics*

## **Vutrisiran-mediated knockdown of transthyretin in patients with ATTR amyloidosis**

Marianna Fontana, Vincent Algalarrondo, Pablo Garcia-Pavia, Mathew S Maurer, Julian D  
Gillmore, Francesco Cappelli, Kiranmai Kolachana, Xiuqing Gao, Satyawar Jadhav, Nitin  
Mehrotra, Gabriel Robbie, Prajakta Badri

**Corresponding author:** Dr. Marianna Fontana, MD, PhD, National Amyloidosis Centre,  
Division of Medicine, University College London, Royal Free Hospital, Pond Street, London,  
United Kingdom. Email: [marianna.fontana@nhs.net](mailto:marianna.fontana@nhs.net)

## **Supplementary appendix**

### **Contents**

|                                                                                                                                     |   |
|-------------------------------------------------------------------------------------------------------------------------------------|---|
| Supplementary methods.....                                                                                                          | 2 |
| Supplementary results.....                                                                                                          | 2 |
| Area under the curve for TTR remaining at trough .....                                                                              | 2 |
| PK/PD modeling population .....                                                                                                     | 2 |
| Supplemental Table 1: Demographics and baseline characteristics of patients with ATTRv-PN<br>(HELIOS-A) and ATTR-CM (HELIOS-B)..... | 3 |
| Supplemental Table 2: Demographics and baseline characteristics of the PK/PD model analysis<br>population by study .....            | 5 |
| References.....                                                                                                                     | 6 |

## **Supplementary methods**

Blood samples for serum TTR analysis were collected at baseline and Days 1, 3, 8, 15, 22, 29, 43, 57, 90, 118, 146, 174, 202, 230, 258, 286, and 314 post-dose in Study 001; at baseline and Weeks 3, 6, 12, 18, 24, 30, 36, 36–39 (Month 9), 39, 42, 48, 54, 60, 66, 72, 78, and 79–80 (Month 18) in HELIOS-A; and at baseline and Weeks 6, 12, 24, 36, 48, 60, 72 (Month 18), 84, 96, 108, 120, and 132 (Month 30) in HELIOS-B.

Blood samples for anti-drug immunoglobulin G or immunoglobulin M antibody testing were collected on Day 1 and Weeks 3, 12, 24, 36, 48, 72, and 79–80 in HELIOS-A, and on Day 1, and Weeks 12, 24, 36, 48, and 108 in HELIOS-B. Samples collected on dosing days were collected within 1 hour pre-dosing.

## **Supplementary results**

### **Area under the curve for TTR remaining at trough**

The median (95% confidence interval) area under the curve ( $AUC_{0-132 \text{ weeks}}$ ) for percent TTR remaining at trough was 2,416 (2,178, 2,778) %\*week for the vutrisiran arm vs 11,531 (11,135, 11,929) %\*week for the placebo arm, with the difference between treatments of - 79% \*week in favor of vutrisiran.

### **PK/PD modeling population**

Data for 80 healthy volunteers from Study 001 (vutrisiran 5 mg [ $n = 6$ ], 25 mg [ $n = 18$ ], 50 mg [ $n = 18$ ], 100 mg [ $n = 6$ ], 200 mg [ $n = 6$ ], or 300 mg [ $n = 6$ ], or placebo [ $n = 20$ ]), 122 patients with ATTRv-PN from HELIOS-A (all vutrisiran 25 mg Q3M), and 641 patients with ATTR-CM (ATTRwt and ATTRv) from HELIOS-B (vutrisiran 25 mg 3QM [ $n = 317$ ] or placebo [ $n = 324$ ]) were used in the PK/PD modeling. Baseline demographics and disease characteristics for the patients who contributed data to the model are shown in Supplemental Table 2.

**Supplemental Table 1** Demographics and baseline characteristics of patients with ATTRv-PN (HELIOS-A) and ATTR-CM (HELIOS-B).

|                                    | <b>HELIOS-A<br/>(N = 122)</b>  | <b>HELIOS-B<br/>(N = 326)</b>    |
|------------------------------------|--------------------------------|----------------------------------|
| Age, median (range), years         | 60 (26–85)                     | 77 (45–85)                       |
| Sex, male, n (%)                   | 79 (64.8)                      | 299 (91.7)                       |
| Ethnicity/race, n (%)              |                                |                                  |
| White                              | 86 (70.5)                      | 277 (85.0)                       |
| Black/African American             | 4 (3.3)                        | 23 (7.1)                         |
| Asian                              | 21 (17.2)                      | 18 (5.5)                         |
| Other/multiple                     | 11 (9.0)                       | 8 (2.5)                          |
| ATTRwt, n (%)                      | NA                             | 289 (88.7)                       |
| ATTRv, n (%)                       | 122 (100)                      | 37 (11.3)                        |
| TTR genotype, n (%)                |                                |                                  |
| V30M                               | 54 (44.3)                      | 4 (1.2)                          |
| Early-onset V30M, <50 years        | 25 (20.5)                      | NA                               |
| Non-V30M                           | 68 (55.7) <sup>a</sup>         | 33 (10.1) <sup>b</sup>           |
| mNIS +7, mean (SD)                 | 60.6 (36.0)                    | NA                               |
| NIS, n (%)                         |                                |                                  |
| <50                                | 78 (63.9)                      | NA                               |
| >50–<100                           | 39 (32.0)                      |                                  |
| ≥100                               | 5 (4.1)                        |                                  |
| PND score, n (%)                   |                                |                                  |
| I                                  | 44 (36.1)                      | NA                               |
| II                                 | 50 (41.0)                      |                                  |
| IIIA                               | 16 (13.1)                      |                                  |
| IIIB                               | 12 (9.8)                       |                                  |
| NAC ATTR stage, <sup>c</sup> n (%) |                                |                                  |
| 1                                  | NA                             | 208 (63.8)                       |
| 2                                  |                                | 100 (30.7)                       |
| 3                                  |                                | 18 (5.5)                         |
| NYHA class, n (%)                  |                                |                                  |
| I                                  | NA                             | 49 (15.0)                        |
| II                                 |                                | 250 (76.7)                       |
| III                                |                                | 27 (8.3)                         |
| 6MWT distance, mean (SD), m        | NA                             | 372.0 (103.7)                    |
| Norfolk QoL-DN, mean (SD)          | 47.1 (26.3)                    | NA                               |
| KCCQ-OS, mean (SD)                 | NA                             | 73.0 (19.4)                      |
| Prior tafamidis use, n (%)         | 53 (43.4)                      | NA                               |
| Baseline tafamidis use, n (%)      | NA                             | 130 (39.9)                       |
| NT-proBNP, pg/mL                   | 1,010.3 (2,148.6) <sup>d</sup> | 2,021 (1,138–3,312) <sup>e</sup> |
| Troponin I, pg/mL                  | 36.7 (121.7) <sup>d</sup>      | 71.9 (44.9–115.9) <sup>e</sup>   |
| Serum TTR, mean (SD), µg/mL        | 206.1 (61.0)                   | 281.4 (91.1)                     |

Adapted from Adams et al. (2023) [1] and Fontana et al. (2025) [2]. <sup>a</sup>Represents 25 different *TTR* mutations. <sup>b</sup>Represents eight different *TTR* mutations. <sup>c</sup>NAC disease stage was defined based on

published criteria (Gillmore et al. 2018 [3]) as: Stage 1 (lower risk), NT-proBNP level  $\leq 3,000$  pg/mL and eGFR of  $\geq 45$  mL/min/1.73 m<sup>2</sup>; Stage 2 (intermediate risk), included all patients who did not meet the criteria for Stages 1 or 3; Stage 3 (higher risk), NT-proBNP  $> 3,000$  pg/mL and eGFR  $< 45$  mL/min/1.73 m<sup>2</sup>. <sup>d</sup>Data are mean (SD). <sup>e</sup>Data are median (IQR).

*6MWT* 6-minute walk test, *ATTR* transthyretin amyloidosis, *ATTR-CM* transthyretin amyloidosis with cardiomyopathy, *ATTRv* variant (hereditary) transthyretin amyloidosis, *ATTRv-PN* variant (hereditary) transthyretin amyloidosis with polyneuropathy, *ATTRwt* wild-type transthyretin amyloidosis, *eGFR* estimated glomerular filtration rate, *IQR* interquartile range, *KCCQ-OS* Kansas City Cardiomyopathy Questionnaire-Overall Summary, *mNIS* +7 modified Neuropathy Impairment Score +7, *NA* not available, *NAC* National Amyloidosis Centre, *NIS* Neuropathy Impairment Score, *Norfolk QoL-DN* Norfolk Quality of Life-Diabetic Neuropathy *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *PND* polyneuropathy disability, *SD* standard deviation, *TTR* transthyretin.

**Supplemental Table 2** Demographics and baseline characteristics of the PK/PD model

analysis population by study.

|                             | <b>Study 001<br/>(N = 80)<sup>a</sup></b> | <b>HELIOS-A<br/>(N = 122)</b> | <b>HELIOS-B<br/>(N = 641)<sup>b</sup></b> | <b>Total<br/>(N = 843)</b> |
|-----------------------------|-------------------------------------------|-------------------------------|-------------------------------------------|----------------------------|
| Age, median (range), years  | 29 (19–44)                                | 60 (26–85)                    | 77 (45–85)                                | 74 (19–85)                 |
| Sex, male, n (%)            | 38 (47.5)                                 | 79 (64.8)                     | 593 (92.5)                                | 710 (84.2)                 |
| Ethnicity/race, n (%)       |                                           |                               |                                           |                            |
| White                       | 41 (51.2)                                 | 86 (70.5)                     | 541 (84.4)                                | 668 (79.2)                 |
| Black/African American      | 10 (12.5)                                 | 4 (3.3)                       | 45 (7.0)                                  | 59 (7.0)                   |
| Asian                       | 23 (28.8)                                 | 21 (17.2)                     | 37 (5.8)                                  | 81 (9.6)                   |
| Other/multiple              | 6 (7.5)                                   | 11 (9.0)                      | 4 (0.6)                                   | 21 (2.5)                   |
| Body weight, mean (SD), kg  | 70.7 (11.8)                               | 70.7 (17.2)                   | 80.9 (14.1)                               | 78.4 (15.0)                |
| ATTRwt, n (%)               | NA                                        | NA                            | 567 (88.5)                                | NA                         |
| ATTRv, n (%)                | NA                                        | 122 (100)                     | 74 (11.5)                                 | NA                         |
| NYHA class, n (%)           |                                           |                               |                                           |                            |
| I                           | NA                                        | NA                            | 581 (90.6)                                | NA                         |
| II/III                      |                                           |                               | 60 (9.4)                                  |                            |
| Tafamidis use, n (%)        | NA                                        | NA                            | 255 (39.8)                                | NA                         |
| NT-proBNP, mean (SD), pg/mL | NA                                        | 1,010.3 (2,148.6)             | 2,398.0 (1,751.0)                         | 2,176.1 (1,889.0)          |
| Serum TTR, mean (SD), µg/mL | 272.2 (56.0)                              | 206.1 (61.0)                  | 280.3 (90.2)                              | 268.8 (87.7)               |

<sup>a</sup>Includes 20 healthy individuals who received placebo. <sup>b</sup>Includes 324 patients with ATTR-CM who received placebo.

*ATTR-CM* transthyretin amyloidosis with cardiomyopathy, *ATTRv* hereditary transthyretin

amyloidosis, *ATTRwt* wild-type transthyretin amyloidosis, *NA* not available, *NT-proBNP* N-terminal

pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *PD* pharmacodynamic, *PK*

pharmacokinetic, *SD* standard deviation, *TTR* transthyretin.

## References

1. Adams D, Tournev IL, Taylor MS, Coelho T, Planté-Bordeneuve V, Berk JL, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid* 2023;30:1–9. <https://doi.org/10.1080/13506129.2022.2091985>
2. Fontana M, Berk JL, Gillmore JD, Witteles RM, Grogan M, Drachman B, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med* 2025;392:33–44. <https://doi.org/10.1056/NEJMoa2409134>
3. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018;39:2799–2806