**Errata to FDA Briefing Document**

Cardiovascular and Renal Drugs Advisory Committee Meeting

September 13, 2023

This memo contains corrections to FDA's briefing information for the September 13, 2023, Cardiovascular and Renal Drugs Advisory Committee Meeting. At this meeting, the Committee will discuss new drug application sNDA 210922/015 for patisiran, submitted by Alnylam Pharmaceuticals, Inc., for the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults.

1) **Correction of Section 2.2 – Pertinent Drug Development and Regulatory History**

**On page 12, first bullet:**

"The Applicant expressed concerns that in the polyneuropathy-predominant population of ATTR amyloidosis, it is difficult to separate functional improvement that is due to neurological improvement from functional improvement due to cardiac improvement."

Should be revised to read

"Division of Cardiology and Nephrology expressed concerns that in the polyneuropathy-predominant population of ATTR amyloidosis, it is difficult to separate functional improvement that is due to neurological improvement from functional improvement due to cardiac improvement. Based on the design of the APOLLO trial (subjects enrolled in this study had symptomatic neuropathy) the study would not support an indication for the treatment of cardiomyopathy in hATTR (ATTR-CM)."

2) **Correction of KCCQ sensitivity analysis with control-based MI of missing data**

   a. **On page 23 and 24, Table 7 titled "Sensitivity Analyses of Mean Change from Baseline at Month 12 in KCCQ-OSS".**

The revised sensitivity analysis results of "Change from baseline at Month 12 from an ANCOVA Model, with control-based MI of missing data" are as follows (bolded):

| Statistic | Patisiran N=181 | Placebo N=178 |
|---|---|---|
| Baseline | | |
| n | 181 | 178 |
| Mean (SE) | 69.8 (1.6) | 70.3 (1.6) |
| Median (Q1, Q3) | 71.4 (53.9, 88.5) | 72.4 (56.5, 88.8) |

| Statistic | Patisiran N=181 | Placebo N=178 |
|---|---|---|
| Change from baseline at Month 12 estimated from MMRM model (included all available assessments) | | |
| LS mean (SE) | 0.4 (1.3) | -3.4 (1.3) |
| LS mean difference (95% CI) | 3.8 (0.3, 7.3) | |
| Nominal p-value | 0.03 | |
| Change from baseline at Month 12 from ANCOVA Model, with control-based MI of missing data | | |
| LS mean (SE) | **0.4 (1.3)** | **-3.3 (1.3)** |
| LS mean difference (95% CI) | **3.7 (0.1, 7.2)** | |
| Nominal p-value | **0.04** | |

**b. On page 23, the last paragraph:**

We also performed a sensitivity analysis with all available KCCQ-OSS (not treating assessments obtained on or after the onset of COVID-19 SAEs as missing) using control-based MI to impute missing data, and conducted an analysis of covariance. On this sensitivity analysis, the LS mean difference in KCCQ-OSS between patisiran and placebo was 2.8 (95% CI -2.5, 8.1) at Month 12 (Table 7).

Should be revised to:

We also performed a sensitivity analysis with all available KCCQ-OSS (not treating assessments obtained on or after the onset of COVID-19 SAEs as missing) using control-based MI to impute missing data and conducted an analysis of covariance. On this sensitivity analysis, the LS mean difference in KCCQ-OSS between patisiran and placebo was **3.7 (95% CI 0.1, 7.2)** at Month 12 (Table 7).