**Indirect treatment comparison (ITC) of the efficacy of vutrisiran and tafamidis for hereditary transthyretin-mediated amyloidosis with polyneuropathy**

**Appendix**

**1.0 Feasibility of ITCs and addressing differences between the studies**

A review of available documentation and published results from the HELIOS-A, APOLLO, and Fx-005 studies was conducted to become familiar with the trials and to assess the feasibility of conducting ITCs. For the HELIOS-A study, the trial protocols and statistical analysis plans were reviewed. For the APOLLO study, the publication by Adams et al. (2018) [1] and the trial protocol were reviewed. For the Fx-005 trial, the following documents were reviewed: Coelho et al. (2012) [2]; Keohane et al. (2017) [3]; the European Medicines Agency (EMA) (2013) summary of product characteristics for tafamidis [4]; and the EMA (2011) public assessment report for tafamidis [5].

The specific aims of the feasibility assessment were to evaluate cross-trial similarities and differences in study design and to inform planning of the ITC analyses, if deemed feasible. This included reviewing, for all trials, the inclusion/exclusion (I/E) criteria, the measured and reported patient baseline characteristics, the outcome definitions and assessments, the reported results, and the analytic approaches.

Based on this assessment, ITCs were deemed feasible for vutrisiran and tafamidis using the available study data. There were some differences in the I/E criteria, baseline characteristics, trial design, and outcomes and definitions that may be addressed using the individual patient-level data for the HELIOS-A and APOLLO studies. The differences and approaches to address them are summarized below.

**1.1 Differences in I/E criteria and study design in Fx-005, HELIOS-A, and APOLLO**

The Fx-005 trial only allowed for inclusion of patients with the *V30M* *TTR* variant and it is assumed that only Familial Amyloid Polyneuropathy (FAP) Stage 1 patients were included, while the HELIOS-A and APOLLO studies allowed for the inclusion of patients with Polyneuropathy Disability (PND) Stage ≤ IIIb (equivalent to FAP Stage 1 and 2) and any *TTR* variant. These differences can be partially accounted for by focusing the ITC on HELIOS-A and APOLLO subpopulations that are more similar to the Fx-005 population. In terms of study design, the HELIOS-A study is an open-label trial designed to establish vutrisiran’s efficacy profile, using the external placebo group from the APOLLO study as the comparator. The Fx-005 trial is a randomized, placebo-controlled study of tafamidis vs. placebo. Since the patients were not randomized to the vutrisiran (from HELIOS-A) vs. placebo-treated (from APOLLO) groups, there may be baseline differences between these arms for which adjustments should be considered. This is discussed in Section 1.2.1.

**1.2 Differences in the distributions of baseline characteristics**

**1.2.1 Differences between the vutrisiran arm of the HELIOS-A study and the placebo arm of the APOLLO study**

ITCs commonly use data from randomized, placebo-controlled trials of each treatment of interest. An indirect treatment effect estimate is obtained by comparing the relative magnitude of the differences between each treatment of interest and a common comparator, usually placebo (i.e. difference between treatment A and treatment B = [difference between treatment A and placebo] – [difference between treatment B and placebo]). When each of the trials are randomized and have concurrent placebo arms, the unadjusted treatment difference relative to placebo in each study is unbiased, as randomization ensures that baseline characteristics, on average, will be similar between the treatment and placebo groups.

As described in Section 2.3 of the Methods, HELIOS-A was designed to minimize cross-study differences with APOLLO. This enabled robust cross-study comparison between vutrisiran and the external placebo group from APOLLO. HELIOS-A and APOLLO used similar I/E criteria, overlapping study sites, and enrolled similar proportions of patients with key baseline characteristics. As a result, HELIOS-A and APOLLO study populations were largely overlapping and are clinically comparable. In the ITC reported here, any potential remaining differences in patient baseline characteristics between HELIOS-A and APOLLO were addressed by calculating treatment effects with adjustment based on propensity scores estimated from the pre-specified sensitivity analyses of the HELIOS-A study, using regression adjustment for continuous outcomes and stabilized inverse probability weighting for binary outcomes. The ITC of vutrisiran vs. tafamidis was based on comparing the adjusted differences between vutrisiran and placebo based on HELIOS-A and APOLLO study data, to the unadjusted difference between tafamidis and placebo from Fx-005.

**1.2.2 Differences between the HELIOS-A and Fx-005 studies**

The distribution of several baseline characteristics differed between the Fx-005 trial and the vutrisiran arm of the HELIOS-A study. Compared to Fx-005, the vutrisiran arm in HELIOS-A included:

* older patients (mean age: 58 vs. 39)
* a larger proportion of male patients (65% vs. 46%)
* a smaller proportion of patients with *V30M* variant (44% vs. 100%)
* a larger proportion of patients from North America (22% vs. 0%)
* a smaller proportion of patients with FAP Stage 1 (70% vs. 100%)
* a larger proportion of patients with prior treatment (59% vs. 0%)
* patients with worse quality of life (QOL) (mean Norfolk Quality of Life – Diabetic Neuropathy questionnaire [Norfolk QOL-DN] scores: 47 vs. 29)

The magnitude of these differences is driven by the systematic differences in I/E criteria of the Fx-005 trial as presented in **Supplementary Table 1**. **Supplementary Table 2** summarizes the differences in baseline and disease characteristics across HELIOS-A, APOLLO, and Fx-005, and **Supplementary Table 3** summarizes the adjusted baseline characteristics across these studies.

**Supplementary Table 1. Overview of the HELIOS-A and Fx-005 studies**

|  | **HELIOS-A study** | **Fx-005 study** |
| --- | --- | --- |
| **Design** | Multicenter, randomized, open-label, phase 3 study of vutrisiran | Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of tafamidis |
| **Study arms** | * Subcutaneous vutrisiran (25 mg, every 3 months)
* Intravenous patisiran (reference comparator, 0.3 mg/kg of body weight, every 3 months)
* Placebo (external comparator from APOLLO study)
 | * Oral tafamidis (20 mg, once daily)
* Placebo
 |
| **Key inclusion criteria**a | * 18 – 85 years of age
* Diagnosis of ATTRv amyloidosis with documented *TTR* variant
* Karnofsky Performance Status ≥60% (equivalent to >50%)
* PND score ≤ IIIb (equivalent to FAP Stage 1 and Stage 2)
* Neuropathy Impairment Score of 5 – 130
 | * 18 – 75 years of age
* Diagnosis of ATTRv amyloidosis with documented *V30M* *TTR* variant
* Karnofsky Performance Status ≥50% (equivalent to >40%)
 |
| **Key exclusion criteria** | * Prior liver transplant or likely to undergo liver transplant during the 18-month treatment period
* Known non-ATTRv forms of amyloidosis or clinical evidence of leptomeningeal amyloidosis
* New York Heart Association heart failure classification >2 (equivalent to ≥3)
 | * Prior liver transplantation
* Has known primary amyloidosis
* Has New York Heart Association heart failure classification ≥3
 |
| **Sample size** | * Vutrisiran: 122
* Patisiran: 42
 | * Tafamidis: 64
* Placebo: 61
 |
| **Follow-up duration (months)** | 18 | 18 |
| **Study visits (months)** | 9 and 18b | 6, 12, and 18 |
| **Primary endpoints** | * Change from baseline in mNIS+7Alnylam at month 9 (for the United States, Japan, and Brazil) and at month 18 (for the European Union) vs. placebo
 | * Improvement or stabilization in NIS-LL (NIS-LL Responder) (increase from baseline in NIS-LL <2 points or any decrease) at month 18
* Change from baseline in Norfolk QOL-DN total scoreat month 18
 |
| **Selected secondary endpoints** | * Change from baseline in Norfolk QOL-DN total score at months 9 and 18 vs. placebo
 | * Change from baseline in mBMIC at month 18
* Change from baseline in NIS-LL at month 18
 |
| **Selected exploratory endpoints** | * Change from baseline in mBMIC at months 9 and 18 vs. placebo
 |  |

ATTRv: hereditary transthyretin-mediated; FAP: Familial Amyloid Polyneuropathy; mBMI; modified Body Mass Index; mNIS+7Alnylam: modified Neuropathy Impairment Score +7 (Alnylam version); NIS-LL: Neuropathy Impairment Score–Lower Limbs; Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Polyneuropathy PND: polyneuropathy disability; *TTR*: transthyretin; *V30M*: valine to methionine variant at amino acid 30.

a FAP Stage 1 is not explicitly an inclusion criterion in Fx-005. However, it is assumed that the entire Fx-005 population was FAP Stage 1. Tafamidis was approved for treating transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy in the European Union, largely on the basis of this trial [5]. The European Medicines Agency specified that 126/128 (98%) patients in Fx-005 had FAP Stage 1 disease [4], although it is unclear how this was ascertained.

b In situations where a month 9 or month 18 efficacy visit was unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic, assessments were completed within 6 months after the intended time point (i.e. up to month 15 or month 24, respectively) after consultation with the Medical Monitor.

C mBMI value = (weight [kg] / height [m2]) x (albumin [g/L]); higher values indicate more favorable nutritional status.

**Supplementary Table 2. Baseline characteristics and disease characteristics of patients with FAP Stage 1 in the APOLLO,HELIOS-A, and Fx-005 studies**

|  | **APOLLO** **FAP Stage 1 subgroup** | **HELIOS-A** **FAP Stage 1** **subgroup** | **Fx-005****ITT population** |
| --- | --- | --- | --- |
|  | **Placebo** **(*n*=37)** | **Vutrisiran** **(*n*=85)**  | **Placebo** **(*n*=61)** | **Tafamidis** **(*n*=64)** |
| **Age, mean (SD), years** | 60.1 (11.2) | 54.4 (13.3) | 38.4 (12.9) | 39.8 (12.7) |
| **Sex, male *n* (%)** | 25 (67.6) | 55 (64.7) | 26 (43) | 32 (50) |
| ***TTR* variant *V30M*, *n* (%)** | 20 (54.1) | 41 (48.2) | 61 (100) | 64 (100) |
| **Disease duration, mean (SD), years** | 2.4 (3.0) | 4.0 (4.2) | 2.9 (2.7) | 3.9 (4.0)  |
| **Prior treatment with tafamidis or diflunisal, *n* (%)** | 20 (54.1) | 53 (62.4) | 0 (0) | 0 (0) |
| **mBMI, mean (SD)** | 1027.4 (219.0) | 1080.5 (232.9)  | 1011.5 (212.9) | 1004.6 (165.2) |
| **Norfolk QOL-DN, mean (SD)** | 43.7 (21.2) | 40.4 (24.4) | 30.8 (26.7) | 27.3 (24.2) |
| **NIS-LL, mean (SD)** | 20.9 (11.7) | 21.3 (14.0) | 11.4 (13.5) | 8.4 (11.4) |

FAP: Familial Amyloid Polyneuropathy; mBMI; modified Body Mass Index; NIS-LL: Neuropathy Impairment Score - Lower Limbs; Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Polyneuropathy; SD; standard deviation; *TTR*: transthyretin; *V30M*: valine to methionine variant at amino acid 30.

**Supplementary Table 3. Baseline characteristics and disease characteristics in the full APOLLO and HELIOS-A mITT populations and Fx-005 ITT population**

|  | **APOLLO****full****mITT population** | **HELIOS-A****full****mITT population** | **Fx-005****ITT population** |
| --- | --- | --- | --- |
|  | **Placebo****(*n*=77)** | **Vutrisiran****(*n*=122)** | **Placebo****(*n*=61)** | **Tafamidis****(*n*=64)** |
| **Age, mean (SD), years** | 62.2 (10.8) | 57.8 (13.2) | 38.4 (12.9) | 39.8 (12.7) |
| **Sex, male *n* (%)** | 58 (75.3) | 79 (64.8) | 26 (43) | 32 (50) |
| ***TTR* variant *V30M*, *n* (%)** | 40 (51.9) | 54 (44.3) | 61 (100) | 64 (100) |
| **Disease duration, mean (SD), years** | 2.60 (3.24) | 3.35 (3.69) | 2.9 (2.7) | 3.9 (4.0) |
| **Prior treatment with tafamidis or diflunisal, *n* (%)** | 41 (53.2) | 75 (61.5) | 0 (0) | 0 (0) |
| **mBMI,a mean (SD)** | 989.9 (214.2) | 1057.4 (233.8) | 1011.5 (212.9) | 1004.6 (165.2) |
| **Norfolk QOL-DN, mean (SD)** | 55.5 (24.3) | 47.1 (26.3) | 30.8 (26.7) | 27.3 (24.2) |
| **NIS-LL, mean (SD)** | 34.8 (17.8) | 27.7 (16.9) | 11.4 (13.5) | 8.4 (11.4) |

FAP: Familial Amyloid Polyneuropathy; ITT: intention-to-treat; mBMI: modified Body Mass Index; mITT: modified intention-to-treat; NIS-LL: Neuropathy Impairment Score - Lower Limbs; Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Polyneuropathy; SD; standard deviation; *TTR*: transthyretin; *V30M*: valine to methionine variant at amino acid 30

a mBMI value = (weight [kg] / height [m2]) x (albumin [g/L]); higher values indicate more favorable nutritional status.

**1.3 Differences in key endpoints**

NIS-LL was a co-primary endpoint in Fx-005 but is not among the ranked endpoints in the APOLLO or HELIOS-A studies. As the NIS-LL is made up entirely from subcomponents (i.e. sensations, reflexes, and muscles weakness) of the NIS or mNIS+7 [6], NIS-LL values can be derived for patients in the APOLLO and HELIOS-A studies. In the same way, for the binary measure for NIS-LL (i.e. NIS-LL Responder - improvements or stabilization of NIS-LL based on an increase from baseline of <2 or any decrease), observed proportions for improvements or no change in NIS-LL at month 18 can be estimated for HELIOS-A and APOLLO studies for the comparison with Fx-005.

**2.0 Handling of onset of serious COVID-19 adverse events in HELIOS-A study patients**

HELIOS-A was conducted over the course of the ongoing coronavirus disease 2019 (COVID-19) pandemic (with the first dose administered February 14, 2019, and the 18-month data cut off occurring on August 26, 2021). Patients who experienced a serious COVID-19-related adverse event (AE) may therefore have worsening in general health and wellbeing unassociated with ATTRv amyloidosis or the study drug. As a result, in the primary HELIOS-A study analyses, outcome assessments on or after onset of a serious COVID-19 AE in the vutrisiran arm were censored and considered missing. For these patients, no explicit imputation of missing outcome data was completed. As part of HELIOS-A, a prespecified sensitivity analysis was conducted to examine whether the inclusion of data censored due to serious COVID-19 AEs impacted the results of the primary analysis. This analysis indicated that study outcomes were consistent with or without censoring of data collected on or after serious COVID-19 AEs. In light of this, the ITC analyses reported here are based similarly on results from adjusted MMRM models for 18-month changes that do not explicitly impute any outcome data in the event of censoring due to a serious COVID-19 AE for patients in HELIOS-A.

**3.0 Application of the Bucher method in the ITC**

**3.1 Change in NIS-LL, Norfolk QOL-DN, and mBMI**

For changes in NIS-LL, Norfolk QOL-DN, and mBMI at 18 months, the propensity-score adjusted estimate of the difference in mean change between the vutrisiran arm in HELIOS-A and the placebo arm in APOLLO were used in the Bucher analysis. This difference was then compared against the published difference in mean change between tafamidis and placebo from the Fx-005 study.

**3.2 NIS-LL Responder at month 18**

The proportion of vutrisiran arm patients in HELIOS-A and placebo arm patients in APOLLO deemed to be NIS-LL Responders at 18 months was calculated. Stabilized inverse probability of treatment weightings were used to balance baseline differences between vutrisiran and placebo arms in the calculation of risk difference (RD), odds ratio (OR), and risk ratio (RR) for vutrisiran vs. placebo. Vutrisiran patients had weights given by P(T=1)/P(T=1|X=x), and placebo patients had weights given by P(T=0)/P(T=0|X=x) = (1- P(T=1))/(1 - P(T=1|X=x)), where T=1 indicates being in the vutrisiran arm, T=0 indicates being in the placebo arm, and X=x indicates a vector of baseline covariates for a given patient. P(T=1|X=x) is the propensity score of being in the vutrisiran arm for each patient and was based on the propensity score model fit in the pre-specified sensitivity analyses of the HELIOS-A study. The adjusted RD, RR, and OR were then compared to the corresponding quantities for tafamidis vs. placebo from Fx-005 using standard formulae for the Bucher method to obtain the estimated indirect treatment effect on each of these effect measures.

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