Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on a Finding in the Procedure of Routine Practice Data Collection and Evaluations according to Section 35a, paragraph 3b SGB V: Onasemnogene abeparvovec (spinal muscular atrophy) – review of study protocol and statistical analysis plan

of 6 June 2024

At its session on 6 June 2024, the Federal Joint Committee (G-BA) decided the following in the procedure of routine practice data collection and evaluations according to Section 35a, paragraph 3b SGB V for the active ingredient onasemnogene abeparvovec (spinal muscular atrophy):

I. It is established that the pharmaceutical company has appropriately implemented the required amendments to the study documents specified in the declaratory resolution of 20 October 2022 and in the amendment resolution of 21 September 2023. The submitted, revised versions of the study protocol (version 4.01 of 26 January 2024) and the statistical analysis plan (SAP) (version 4.00 of 8 January 2024) require further adaptation. The routine practice data collection can therefore only be continued under the condition that the following adaptations to the study protocol (version 4.01 of 26 January 2024) and to the SAP (version 4.00 of 8 January 2024), which are deemed mandatory for the implementation of the requirements pursuant to Section 58, paragraph 1, no. 1 VerfO, are made:

a) Interpretation of the data (confounder): Ulnar CMAP

In the 4th version of the study documents, the "ulnar Compound Muscle Action Potential (CMAP)" intended for a sensitivity analysis for confounder adjustment was cancelled as a confounder due to missing data. The justification for the cancellation is inadequate. The consequence of the missing data and the resulting lack of sensitivity analysis must be taken into account when interpreting the results.

This procedure must be recorded in the study documents.

b) Interpretation of the data (confounder): CHOP-INTEND

In the 4th version of the study documents, the new category ("n.a.") was added for the confounder "Children's Hospital of Philadelphia Infant Test of Neuromuscular

Disorders (CHOP-INTEND)" due to developments in the conduct of the study. The justification is inadequate. If the category "n.a." has been added in order to take into account those patients for whom the CHOP-INTEND is not collected, it must be ensured that missing values are imputed for patients for whom the CHOP-INTEND can theoretically be collected.

The procedure must be described accordingly in the study documents.

c) Data evaluation: Confounding in subgroup analyses

In the 4th version of the study documents, a passage on the handling of confounding in subgroup analyses was deleted in which it was stated that for each subgroup analysis based on a confounder, a new propensity score weighting is determined according to the procedures described in the SAP, whereby the confounder itself is not part of the logistic regression. The deletion is inappropriate as this could pose a risk of bias.

An appropriate procedure for dealing with confounding in subgroup analyses must be added to the study documents.

d) Data evaluation: Sensitivity analyses

In the 4th version of the study documents, there are inconsistencies between the study protocol and the SAP in the information on the sensitivity analyses. Furthermore, the additional sensitivity analysis in the SAP to investigate "carry-over" effects of nusinersen, in which the time of the theoretical next application of nusinersen is defined as the time of censoring, was cancelled due to the addition of risdiplam to the comparator. This is inappropriate.

The sensitivity analysis for the consideration of "carry-over" effects of nusinersen upon change in treatment shall therefore be retained in the study documents, and the inconsistencies in the information on the sensitivity analyses shall also be eliminated.

e) Data evaluation: Confounder adjustment

For the main analyses, the pharmaceutical company is planning a confounder adjustment using the Standardised Mortality Ratio Weighting (SMRW) and the Fine Stratification Weights (FSW), which refer to the Average Treatment Effect among Treated (ATT). The planned analytical method is inappropriate.

Suitable analytical methods relating to the Average Treatment Effect (ATE) must be included in the study documents.

f) Data evaluation: Dealing with missing values for confounders

The method of multiple imputation using Fully Conditional Specification (FCS) / Chained Equations (MICE) for missing values for confounders described in the study documents is suitable in principle. However, it is not clear from the information how the multiple imputation is to be specifically combined with the estimation of the propensity score and the subsequent effect estimate for the endpoints.

The exact procedure is to be specified by the pharmaceutical company in the study documents.

g) Data evaluation: final sample size estimate

In Addendum 4 of the current study protocol version 4.01, the pharmaceutical company submits an updated sample size estimate and a futility check. At the same time, however, it points to relevant uncertainties that make it impossible to make a final sample size estimate or to check the futility of the routine practice data collection at this point in time.

The reasons given by the pharmaceutical company with regard to the uncertainty of the development of patient numbers in the further course of the routine practice data collection are understandable. The study protocol must stipulate that a final sample size estimate and a futility check must be performed for the 2nd interim analysis.

In order to avoid inconsistencies, the pharmaceutical company must check whether the need for changes in the study protocol described here leads to corresponding subsequent changes in the SAP and vice versa.

II. The revised study protocol and the revised SAP are to be submitted to the G-BA by 4 August 2025.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 June 2024.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 6 June 2024

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken