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, statistical analysis plan and interim analyses

of 4 December 2025

At their session on 4 December 2025, 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 completed the required need for adaptation for the implementation of the routine practice data collection in the study documents.

II. Taking into account the need for adaptation specified in the declaratory resolution of 6 June 2024, the information contained in the submitted, revised versions of the study protocol (version 5.01 of 1 August 2025) and the statistical analysis plan (SAP) (version 5.01 dated 1 August 2025) and the review of the procedure as part of the 2nd interim analysis, the following need for adaptation, which is considered absolutely necessary for the implementation of the requirements under Section 58, paragraph 1, number 1 VerfO, results for the planned evaluations of the data collected by the routine practice data collection in the context of the new benefit assessment:

a) Data evaluation: Confounder

When dealing with confounders with over 50% of missing values, the procedure described for the CHOP-INTEND (no imputation of missing values and no consideration of this confounder in the propensity score model) should generally be applied. However, the uncertainty caused by the non-inclusion of relevant confounders must be taken into account when interpreting the data collected by the routine practice data collection, for example by defining a specific threshold value for the shifted null hypothesis (less than 0.5 or greater than 2).

b) Data evaluation: Confounding in subgroup analyses

Furthermore, an appropriate procedure for dealing with confounding in subgroup analyses must be defined in advance for the evaluation of the data collected by routine practice data collection.

c) Data evaluation: Confounder adjustment

In the study documents, there is a discrepancy between the schematic representation in the flowchart and the description of the procedure in the continuous text with regard to the decision as to whether a naive comparison should be made after review of the balance using standardised mean difference (SMD) after weighting. It must be ensured that the procedure defined in the text (planned naive comparison) is applied for the evaluations to be presented.

The procedure of dichotomising confounders with several categories if the regression models do not converge must be pre-specified and justified. This includes both the description of the situations in which dichotomisation is carried out and the specific selection of the merged categories. In order to justify the chosen procedure, it is inappropriate to refer to the data basis of a previous (interim) analysis. For the final analysis, the decision to dichotomise the confounders according to the pre-specification must be made on the basis of the data then available.

In the event that the SMDs < 0.1 for all confounders of the unweighted study populations, a sensitivity analysis, which is based on a regression analysis and in which the confounders are included as adjustment variables, should be performed in addition to the naive comparison.

d) Data evaluation: Dealing with missing values for confounders

The changes made to the planned imputation procedure in the study documents are in principle appropriate. However, it is not clear from the information provided whether the linking of the imputation procedure with the propensity score method is a within or across approach. This must be determined taking into account the balance analysis and overlap in connection with the MICE (multiple imputation using chained equations) method.

e) Data evaluation: Counting data

The negative binomial model must be used for evaluation of the counting data. A Poisson model can be performed as a sensitivity analysis.

f) Data evaluation: Sensitivity analyses

If there are relevant uncertainties in the data quality due to limitations in the source data verification of individual patients, sensitivity analyses must be carried out excluding these patients.

Appropriate sensitivity analyses excluding data after treatment switching must be presented for all endpoints.

g) Data evaluation: IPD meta-analysis

As planned according to the study documents, the data source must be taken into account in the analysis for the IPD (individual patient data) meta-analysis.

h) Data evaluation: Treatment and treatment duration of the subjects enrolled

For the evaluations of the data collected by the routine practice data collection, separate information must be provided on how many of the patients in the comparator

arm were treated with nusinersen or risdiplam. In addition, information on the durations of observation and treatment switching before and after imputation, and adjustment using propensity score must be provided.

i) Data evaluation: Analysis at registry level

If different weighting methods are used for the analysis at registry level (including meta-analytic summary) and the IPD meta-analysis, the effect estimates from all available weighting methods must be calculated and presented for both registries in order to increase the interpretability of the results.

j) Data evaluation: Endpoints

Any discrepancies between the p value based on the score test of the IPD meta-analysis and the 95% CI in the results on individual endpoints should be discussed.

For the endpoint of achievement of the respective motor milestone, an additional operationalisation is to be carried out as a combined analysis of the achievement and maintenance of the respective motor milestone. For this purpose, evaluations are to be carried out as responder analyses with a follow-up period of 36 months. In addition, descriptive data on the percentages of patients, who:

- have achieved the respective milestone at the start of the study and maintained it in the course of the study,
- have achieved the respective milestone at the start of the study and lost it in the course of the study,
- have not achieved the respective milestone at the start of the study and have achieved it in the course of the study,
- have not achieved the respective milestone at the start of the study and have not achieved it in the course of the study,
- have not achieved the respective milestone at the start of the study and have initially achieved it in the course of the study and subsequently lost it, must be provided.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 4 December 2025.

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

Berlin, 4 December 2025

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

Prof. Hecken