Gemeinsamer Bundesausschuss

Justification

on the Resolution of the Federal Joint Committee (G-BA) on the 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

Contents

1. Legal basis

According to Section 35a, paragraph 3b, sentence 1 SGB V, the Federal Joint Committee (G-BA) can demand the pharmaceutical company to submit routine practice data collections and evaluations for the purpose of the benefit assessment within a reasonable period of time for the following medicinal products:

1. in the case of medicinal products authorised to be placed on the market in accordance with the procedure laid down in Article 14, paragraph 8 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4, 7.1.2019, p. 24), or for which a marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No 726/2004; and
2. for medicinal products approved for the treatment of rare diseases under Regulation No. 141/2000.

According to Section 35a, paragraph 3b, sentence 10 SGB V in conjunction with Chapter 5 Section 60 Rules of Procedure of the
G-BA (VerfO), the G-BA review the data obtained and the obligation to
collect data at regular intervals, at least every eighteen months.

2. Key points of the resolution

At their session on 4 February 2021, the G-BA decided on the requirement of routine data collection and evaluations for the active ingredient onasemnogene abeparvovec in accordance with Section 35a, paragraph 3b, sentence 1 SGB V.

In order to check whether the requirements of the G-BA for the routine practice data collection and evaluations of the data obtained have been implemented, the pharmaceutical company submitted the revised versions of the study protocol and the statistical analysis plan (SAP) (version 3.01 of 13 July 2022) to the G-BA in due time on 1 August 2022. The study documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG).

By G-BA's declaratory resolution of 20 October 2022, the pharmaceutical company was notified of the adjustments to the study protocol and the SAP (version 3.01 of 13 July 2022) that were considered necessary. By G-BA's amendment resolution of 21 September 2023, an amendment to the comparator for the requirement of routine practice data collection and evaluations for the active ingredient onasemnogene abeparvovec was also adopted. The amendment resolution stipulates that the change to the comparator is to be implemented by the pharmaceutical company as part of an addendum to the study protocol and to the statistical analysis plan for the RPDC study and submitted for review.

The pharmaceutical company submitted the revised drafts for a study protocol and an SAP to the G-BA in due time by 2 February 2024. The revised draft study protocol and SAP were reviewed by the G-BA along with IQWiG.

It was established by resolution of 6 June 2024 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) required further adaptation. The resolution required that the revised study documents be submitted to the G-BA for review.

The pharmaceutical company submitted the revised drafts for a study protocol and an SAP to the G-BA in due time by 2 August 2025. The revised draft study protocol and SAP were reviewed by the G-BA along with IQWiG.

At the same time, the procedure for the data collected by routine practice data collection was reviewed as part of the interim analysis 54 months after the date of resolution. The present declaratory resolution specifies and justifies the adaptations - considered absolutely necessary as a result of the reviews - for the planned evaluations of the data collected by routine practice data collection for the new benefit assessment.

On the absolutely necessary adaptations in detail:

a) Interpretation of the data: Confounder

With regard to the potential confounder CHOP-INTEND, the study documents elaborate that missing values are not imputed and this confounder is not taken into account in the propensity score model due to over 50% of missing values at baseline.

The procedure described for CHOP-INTEND is appropriate and should therefore generally be applied when dealing with missing values for confounders with over 50% of missing values. 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. While the textual description points to a planned naive comparison if one (or more) confounders have an SMD > 0.25 after applying the propensity score method, this is not clear from the flow chart. It must be ensured that the procedure defined in the text 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 evaluation of the counting data was changed in the study documents. The statistical model for the effect estimation was changed from a negative binomial model to a Poisson model. It remains unclear why these changes were made, especially since the negative binomial model is the more appropriate model in the present setting.

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. According to current planning, these sensitivity analyses are only carried out for time-to-event analyses.

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

The p value based on the score test of the IPD meta-analysis is implausible for the results on the endpoint "time to achieve independent sitting" in research question 1 (pre-symptomatic patients with ≤ 2 SMN2 copies). This is shown by the fact that the 95% CI is just above 1 and the p value is clearly lower than the significance level of $\alpha = 0.05$. 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.

The currently planned operationalisation for the endpoint "loss of motor milestones" is methodologically problematic. The majority of patients are at risk of not reaching motor milestones at the start of the study. Accordingly, they can only be at risk of losing the motor milestones in the course of RPDC (after achievement of the respective motor milestone). No adequate adjustment is possible as no assessment of confounders is made for these patients at this point in time (new baseline survey for these patients).

For the endpoint of achievement of the respective motor milestone, a combined analysis of the achievement and maintenance of the respective motor milestone as an additional operationalisation is therefore considered expedient. 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.

3. Process sequence

In order to check whether the requirements of the G-BA for routine data collection and evaluations for the active ingredient onasemnogene abeparvovec have been implemented as specified in the resolution of 6 June 2024, the pharmaceutical company submitted revised drafts of a study protocol and a SAP to the G-BA. The documents were reviewed by the G-BA with the involvement of IQWiG.

The issue was discussed in the working group WG RPDC and in the Subcommittee on Medicinal Products.

At their session on 4 December 2025, the plenum decided on the outcome of the review regarding the submitted study protocol (version 5.01 of 1 August 2025) and the statistical analysis plan (SAP) (version 5.01 of 1 August 2025) as well as the interim analysis 54 months after the date of resolution.

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	6 November 2025 17 November 2025	Consultation on the review of study documents (study protocol and SAP) and the interim analysis
Subcommittee on Medicinal Products	25 November 2025	Consultation on the review of study documents (study protocol and SAP) and the interim analysis
Plenum	4 December 2025	Adoption of the resolution on the review of study documents (study protocol and SAP) and the interim analysis

Berlin, 4 December 2025

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

Prof. Hecken