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 and statistical analysis plan

of 6 June 2024

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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.

2. Key points of the resolution

At its 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 drafts for a study protocol and an SAP were reviewed by the G-BA along with the Institute for Quality and Efficiency in Health Care (IQWiG).

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.

On the one hand, this need for adaptation results from changes or adjustments made by the pharmaceutical company in the present 4th version of the study documents, which go beyond the need for changes set out in the declaratory resolutions, thus entailing consequential changes, and on the other, due to a planned methodological approach with regard to confounder adjustment during data evaluation.

This declaratory resolution defines and justifies the further adjustments to the study protocol (version 4.01 of 26 January 2024) and to the SAP (version 4.00 of 8 January 2024) that are considered necessary.

2.1 Necessary adjustments to study protocol and statistical analysis plan

On the necessary adjustments in detail:

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, for example with the shifted null hypothesis.

This must be recorded in the study documents.

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

In the 4th version of the study documents, a new category ("n.a.") was added for the confounder "Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)". The pharmaceutical company states that it has introduced these due to developments in the conduct of the study. However, the methodology and results of the 1st interim analysis do not list the category "n.a.". The justification for the inclusion of the new category 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 procedure described in version 3.01 was appropriate. The deletion of the information on dealing with confounding in subgroup analyses should be reversed, as this could pose the risk of bias. An appropriate procedure for dealing with confounding in subgroup analyses must be added to the study documents. As an example of how confounding is dealt with in subgroup analyses described in the literature, reference is made to a publication by Wang et al. from 2017[1].

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. For example, the SAP lists sensitivity analyses for motor function endpoints that are not specified in the study protocol. 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. However, it is currently unclear how high the percentage of patients treated with nusinersen will be in the comparator arm at the end of study. Since the sensitivity analysis is all the more relevant the higher the percentage of patients treated with nusinersen, the cancellation 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 ATT describes the effect in the patient population treated with the intervention. When planning a non-randomised study, the target population should be recruited according to a target trial emulation based on clear inclusion and exclusion criteria that apply to both treatment groups, so that a patient population that is as

1 Wang SV, He M, Jin Y et al. A review of the performance of different methods for propensity score matched subgroup analyses and a summary of their application in peer-reviewed research studies. Pharmacoepidemiol Drug Saf 2017; 26(12): 1507-1512.

representative as possible is used for the analyses[2]. The corresponding effect in the target population corresponds to the Average Treatment Effect (ATE). The planned analytical method is therefore 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. This concerns the estimation of balance and overlap as well as the model selection for the propensity score procedure.

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 out relevant uncertainties with regard to an updated sample size estimate, among other things, due to the introduction of newborn screening for SMA in Germany, which means that a final sample size estimate as well as a futility check of the routine practice data collection are infeasible at the present 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.

2.2 Deadline for submission of the revised study protocol and statistical analysis plan

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

When submitting the revised version of the SAP and the study protocol, the pharmaceutical company must ensure that the changes made can be completely and clearly understood. For

2 Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomised Trial Is Not Available. Am J Epidemiol 2016; 183(8): 758-764.

this purpose, a version of the documents must usually be submitted in which the changes have been marked in detail, as well as a current version of the documents without marking the changes. Amendments that do not result from the need for adjustment set out in this resolution and the justification shall be justified separately.

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 20 October 2022 and in the amendment resolution of 21 September 2023, the pharmaceutical company submitted revised drafts of a study protocol and an 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 its session on 6 June 2024, the plenum decided on the outcome of the review regarding the submitted study protocol (version 4.01 of 26 January 2024) and the statistical analysis plan (SAP) (version 4.00 of 8 January 2024).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	15 April 2024 2 May 2024 13 May 2024	Advice on reviewing study documents (study protocol and SAP)
Subcommittee Medicinal products	28 May 2024	Advice on reviewing study documents (study protocol and SAP)
Plenum	6 June 2024	Resolution on the review of study documents (study protocol and SAP)

Berlin, 6 June 2024

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

Prof. Hecken