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 20 October 2022

## 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 authorised 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).

It is established that the pharmaceutical company has not fully implemented the requirements in the study protocol as well as in the SAP for the implementation of the routine practice data collection and evaluations as stated in the declaratory resolution of 20 January 2022.

The classification of the confounder "age at symptom onset" in the sub-populations of symptomatic patients as "very important" instead of "less important", as mandated by the declaratory resolution of 20 January 2022, was not implemented. The pharmaceutical company argues that the classification of the importance of the individual confounders was done by clinical experts and that a change in the classification would lead to a misrepresentation of the classification by the clinical experts. Irrespective of this, the different classification would not have any consequences for the analyses. The G-BA does not agree with this: At the request of the G-BA, a confounder can be classified as "very important" in deviation from the classification of the clinical experts consulted by the pharmaceutical company, without the documentation of the classification by the clinical experts having to be

changed in the study protocol. The classification also has potentially significant consequences for the analyses and the interpretation of results of the sub-populations. Confounders that are classified as "very important" are essential for the adjustment of statistical analyses according to the study protocol. Confounders classified as "less important" should be checked in statistical analyses, but valid results are also valid if individual confounders in this category cannot be checked. The confounder "age at symptom onset" must therefore be classified as "very important".

Furthermore, the planning for sensitivity analyses regarding the data on nusinersen collected in parallel and not in parallel, as required in the G-BA's declaratory resolution of 20 January 2022, was not implemented in the present SAP and study protocol (version 3.01 of 13 July 2022). The pharmaceutical entrepreneur argues that a distinction is no longer made between data collected in parallel and data not collected in parallel, as relatively few patients are included before the start of the compassionate use programme of onasemnogene abeparvovec. The G-BA does not agree with this: The data from the pharmaceutical company's status report suggest that a relevant part of the data on nusinersen considered so far for the RPDC study was collected before the start of data collection on onasemnogene abeparvovec. The required planning for sensitivity analyses regarding parallel and non-parallel data on nusinersen must therefore be implemented.

The submitted version 3.01 of the study protocol and the SAP of 13 July 2022 do not only include changes that resulted from the requirements of the G-BA in the declaratory resolution of 20 January 2022. With regard to further changes, the pharmaceutical company refers to the recommendations of the G-BA described in the justification for the declaratory resolution of 20 January 2022. The pharmaceutical company states that a large number of additions have resulted in particular from the implementation of the explicit recommendation of the G-BA to provide for the RESTORE registry as a secondary data source. However, far-reaching changes were also made beyond the requirements and recommendations of the G-BA. The pharmaceutical company has not clearly and completely labelled all changes. In addition, there are significant inconsistencies in the study protocol and SAP due to the changes made within the documents and between the documents, also with regard to central points of content[1]. The impact of these changes on the RPDC study using the SMArtCARE registry as the primary data source therefore remains unclear. All changes that go beyond the requirements of the G-BA in the declaratory resolution of 20 January 2022 must be reversed accordingly.

When resubmitting the revised version of the study protocol and the SAP, the pharmaceutical company must ensure that the changes made can be completely and clearly understood. For this purpose, a version of the documents must be submitted in which the changes have been marked in detail (e.g., deletion of deleted passages, underlining of added passages), 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 declaratory resolution and the associated justification must be justified separately and must be submitted in a separate addendum to the study protocol or SAP.

1 IQWiG report – No. 1417: Routine practice data collection of onasemnogene abeparvovec: Review of the study protocol and statistical analysis plan 3rd addendum to the mandate A20-61, addendum A22-84, last revised: 06.09.2022.

In addition, it should be noted that the pharmaceutical company's statement that the G-BA made the explicit recommendation to provide the RESTORE registry as a secondary data source for the RPDC study is not appropriate. The corresponding recommendation of the G-BA in the justification for the declaratory resolution of 20 January 2022 reads as follows: "The G-BA recommends that the requirements for the integration of further registries described in the resolution on the requirement of the RPDC be listed in the study protocol and that the necessary references be made to the respective explanations in the study protocol on the RPDC, e.g., on source data verification. Study protocol and SAP for data collection in the SMArtCARE registry could then be the starting point for the integration of other international registries including the RESTORE registry". Instead of a direct integration of the RESTORE registry alone into the study protocol and the SAP and the associated far-reaching changes to these documents, the pharmaceutical company would have to take into account the aforementioned recommendation of the G-BA.

The pharmaceutical company is obliged to make the aforementioned adjustments in the study protocol and in the SAP (version 3.01 of 13. 2022). The revised, final versions of the study protocol and the SAP must be submitted to the G-BA as part of the 1st interim analysis 36 months after date of resolution of the RPDC requirement.

In the event of non-compliance with the conditions, the G-BA reserves the right to reject the data from the study for the routine practice data collection in the subsequent benefit assessment according to Section 35a SGB V for the active ingredient onasemnogene abeparvovec with reference to methodological deficiencies in the collection or to impose other sanctions, up to and including discontinuation of the routine practice data collection, if the conditions are not implemented.

## 3. Process sequence

The pharmaceutical company submitted the revised study protocol and a revised SAP to the G-BA for the purpose of reviewing whether the requirements of the G-BA regarding the routine practice data collection and evaluations for the active ingredient onasemnogene abeparvovec as specified in the resolution of 20 January 2022 have been implemented. 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.

The review has shown that the pharmaceutical company has not fully implemented the requirements in the study protocol as well as in the SAP for the conduct of the routine practice data collection and evaluations mentioned in the declaratory resolution of 20 January 2022, and that further adjustments to the study documents are considered mandatory.

At its session on 20 October 2022, the plenum therefore decided by consensus that the routine practice data collection could only be carried out on the condition that the adjustments to the study documents (version 3.01 of 13 July 2022) mentioned in the resolution and deemed mandatory for the implementation of the requirements pursuant to Section 58, paragraph 1, number 1 VerfO were made.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| WG RPDC | 12 September 2022<br>6 October 2022 | Advice on reviewing study documents (study protocol and SAP) |
| Subcommittee Medicinal products | 11 October 2022 | Advice on reviewing study documents (study protocol and SAP) |
| Plenum | 20 October 2022 | Resolution on the review of study documents (study protocol and SAP) |

Berlin, 20 October 2022

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

Prof. Hecken