Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on the Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Onasemnogene Abeparvovec (Spinal Muscular Atrophy); Requirement of Routine Data Collection and Evaluations

of 4 February 2021

At its session on 4 February 2021, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient onasemnogene abeparvovec as follows:

Onasemnogene abeparvovec

Resolution of: 4 February 2021
Entry into force on: DD MM YYYY
Federal Gazette, BAnz AT DD MM YYYY Bx

Requirement of a routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient onasemnogene abeparvovec in the treatment of:

patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1 or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

1. Requirement of routine data collection and evaluations

With reference to the justification for the necessity of a routine data collection for the active ingredient onasemnogene abeparvovec for the purpose of the benefit assessment, which forms the basis of the resolution initiating the procedure to require a routine data collection of 16 July 2020, the following requirements result:

1.1. Question in accordance with PICO scheme

Population	▪ Pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene ▪ Symptomatic patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1 ▪ Symptomatic patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 2 and up to 3 copies of the SMN2 gene The survey should also include patients in the above patient population who are older than 6 months or 6 weeks at the time of gene therapy with onasemnogene abeparvovec.
Intervention	▪ Onasemnogene abeparvovec The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.
Comparator	▪ Nusinersen The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.

Outcome	Mortality ▪ Deaths Morbidity ▪ Motor functioning (surveyed with age-appropriate instruments) *and* ▪ Achievement of motor development milestones of the WHO *and* ▪ Respiratory functioning (need for [continuous] ventilation) *and* ▪ Bulbar functioning (ability to swallow and speak, need for non-oral nutritional support) *and* ▪ Further complications of the disease (e.g. pain, orthopaedic complications) Side effects ▪ Serious adverse events (SAE) ▪ Adverse events leading to hospitalisation ▪ Serious specific adverse events: Hepatotoxicity, thrombocytopenia, cardiac events, inflammation of spinal ganglion cells, renal toxicity, hydrocephalus

1.2. Type and methodology of data collection

Taking into consideration the question of the routine data collection and the methodological limitations of non-randomised comparisons, the following requirements are placed on the study design and the data source for the present routine data collection.

1.2.1 Study design requirements

- non-randomised comparison of onasemnogene abeparvovec and data on nusinersen collected in parallel, as well as data on nusinersen not collected in parallel within one data source provided that the data not collected in parallel also meet the data quality requirements stated under Section 1.2.2.

1.2.2. Data source requirements

- Use of indication registers as a data source that meet the requirements for the routine data collection and fulfil at least the following quality criteria[1]:
  - Detailed register description (protocol)
  - Exact definition or operationalisation of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints, and confounders
  - Use of standard classifications and terminologies
  - Use of validated standard survey instruments (questionnaires, scales, tests)
  - Training on data collection and recording
  - Implementation of an approved disease-specific core data set
  - Use of exact dates for the patient, the disease, important examinations, and treatments/interventions
  - Clearly defined inclusion and exclusion criteria for register patients

[1] IQWiG Rapid Report A20-61: Concept for a routine data collection – onasemnogene abeparvovec.

- Strategies to avoid unwanted selections during patient inclusion in order to achieve representativeness
- Specifications to ensure completeness of data per survey date and completeness of survey dates
- Source data verification for 100% of patients per survey centre for the primary endpoint and for at least 10% of randomly selected patients per survey centre for all other endpoints over the period since the start of data collection
- Assurance of scientific independence and transparency of the register

- Use of an indication register in which spinal muscular atrophy is treated in accordance with everyday care in Germany or is sufficiently similar to care in Germany

1.2.3 Primary register and integration of further registers

- Use of the SMArtCARE register as primary register provided that the quality criteria mentioned in Section 1.2.2 are fulfilled
- It is also possible to integrate other registers, taking into consideration all the data source requirements mentioned in Section 1.2.2

1.3. Duration and scope of data collection

Taking into consideration the child's developmental process on the basis of the motor milestones in accordance with WHO, the therapy results of onasemnogene abeparvovec and nusinersen as well as the assessment of the sustainability of the motor development achieved, the following patient-related observation period is to be taken into consideration when collecting the routine data:

- Observation of the achievable motor development: until month 36
- Observation of the sustainability of the achieved development: until month 60

As an approximation of the appropriate number of cases for the routine data collection, the following number of cases is assumed as a result of an orienting case number estimate based on the combined endpoint mortality/continuous ventilation:

- Approx. 500 patients (orienting case number estimate)

1.4. Evaluations of the data collection

1.4.1 Study protocol and statistical analysis plan

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out the routine data collection and evaluations. In this context, it shall, in particular, provide the following information in advance with regard to the evaluation of the data:

- Information on the statistical methods and models used as well as naming of the procedures and the criteria used in model selection and fitting
- Information on the expected scope and reasons for missing data as well as measures to avoid missing data and evaluation strategies to deal with missing data
- Information on dealing with implausible data and outliers
- Information on planned sensitivity analyses
- Information on the identification and adequate pre-specified adjustment for confounders
- Information on the investigation of potential effect modifiers

- Information on subgroup analyses based on the copy number of the SMN2 gene for pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene for the purpose of verifying whether a joint evaluation is appropriate
- Information on the extent to which the data on nusinersen collected in parallel and not collected in parallel are suitable for a pooled analysis
- Information on the extent to which data, if any, comparing onasemnogene abeparvovec and nusinersen from different data sources are suitable for a pooled analysis
- Information on dealing with patients who change their medicinal therapy or receive combination therapy
- Information on interim analyses taking into account the requirements under Section 1.4.2 as well as the specifications under Section 2.3
- Information on discontinuation criteria because of futility

1.4.2 Evaluations of the data for the purpose of the benefit assessment

The pharmaceutical company shall submit the following evaluations to the G-BA:

- Interim analyses

  Evaluations of 3 interim analyses are to be presented. The relevant times for the implementation of the interim analyses shall be the times specified in Section 2.3.

  The interim analyses shall be performed according to the specifications in the study protocol and statistical analysis plan. In the process, a check for discontinuation because of futility must also be carried out for each interim analysis.

  On 1. interim analysis 18 months after the date of resolution:

  Based on this interim analysis, a final case number estimate will be made using the more precise effect assumptions that will then be possible. If necessary, this can also be carried out at this time on the basis of other benefit endpoints (such as motor development or a different operationalisation of the need for ventilation) and taking into consideration a shifted hypothesis boundary following the procedure in the concept of the IQWiG[1]. Alternatively, if the pharmaceutical company does not seek superiority in benefit endpoints (such as the aforementioned achievement of motor milestones), a case number can be estimated based on another endpoint. Here, too, shifted hypothesis boundaries must be applied in each case. In the interim analyses, the pharmaceutical company shall present the basis on which it has made the final case number estimate.

The interim analyses are to be prepared based on module 4 of the dossier template, providing the full texts and study documents.

- Final evaluations for the purpose of the renewed benefit assessment

  The final evaluations shall be performed according to the specifications in the study protocol and statistical analysis plan. For the forwarding of the final evaluations to the G-BA, the time specified in Section 3 applies.

The final evaluations are to be prepared in a dossier in accordance with the provisions of Section 9, paragraphs 1 to 7 VerfO of the G-BA.

2. Requirements for checking whether the pharmaceutical company has fulfilled its obligation to carry out routine data collection and evaluations

2.1. Submission of a study protocol and the statistical analysis plan for coordination with the G-BA:

The final drafts for a study protocol and a statistical analysis plan prepared by the pharmaceutical company are to be submitted to the G-BA for approval by 15 August 2021 at the latest.

The G-BA, with the involvement of the IQWiG, will review the study protocol and the statistical analysis plan and send the pharmaceutical company the result in writing within 4 to 6 weeks.

Before submitting the documents to be presented to the G-BA, the pharmaceutical company can, in accordance with Section 35a, paragraph 7 SGB V in conjunction with Section 8 AM-NutzenV, apply for a consultation with the G-BA. The subject of such consultation is, in particular, the drafts for a study protocol as well as for a statistical analysis plan.

2.2 Submission of information on the course of data collection (in particular information on the status of recruitment)

At intervals of 18 months from the date of resolution of the present resolution, the pharmaceutical company shall provide the G-BA with information on

- the number and the respective medicinal treatment of the patients included so far
- patient-related observation times
- possible deviations regarding the expected number of recruits

2.3 Submission of interim analyses

Interim analyses are to be carried out at the following points in time after the date of resolution, and corresponding evaluations are to be submitted to the G-BA, taking into consideration the requirements stated in Section 1.4.2:

- 18 months after date of resolution
- 36 months after date of resolution
- 60 months after date of resolution

3. Deadline for the submission of evaluations of the data collected with the routine data collection

For the implementation of a new benefit assessment, the evaluations of the data collected with the routine data collection must be submitted by 1 July 2027 at the latest.

These evaluations must be submitted in the form of a dossier according to the provisions in Chapter 5, Section 9, paragraphs 1 to 7 VerfO of the G-BA, taking into consideration the requirements of this resolution according to Chapter 5 Section 58 VerfO.

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 4 February 2021.

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

Berlin, 4 February 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken