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Addendum to Commission A21-68[1]

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SMA	spinal muscular atrophy

1 Background

On 28 September 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-68 (Onasemnogene abeparvovec – Benefit assessment according to §35a Social Code Book V) [1].

In the oral hearing on onasemnogene abeparvovec [2], both the pharmaceutical company (hereinafter referred to as "the company") Novartis Gene Therapies and the company Biogen announced to provide subsequent data (regarding onasemnogene abeparvovec and the appropriate comparator therapy [ACT] nusinersen respectively) for the present procedure. These data concern research question 1 of dossier assessment A21-68, the benefit assessment of onasemnogene abeparvovec in comparison with the ACT nusinersen in children with spinal muscular atrophy (SMA) type 1. The G-BA commissioned IQWiG with the assessment of the information subsequently submitted in the commenting procedure.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In the dossier on onasemnogene abeparvovec, the company had presented a comparison of individual arms from studies on onasemnogene abeparvovec and the ACT nusinersen for the patient group with SMA type 1 [3]. It had considered 3 studies for onasemnogene abeparvovec (START, STR1VE-EU, STR1VE-US) and 2 studies for nusinersen ([SHINE]-ENDEAR and [SHINE]-CS3A]). No added benefit of onasemnogene abeparvovec in comparison with nusinersen could be derived from this comparison, partly because there were important differences between the patient populations included in each case. This particularly concerned disease duration (measured as the time from symptom onset to the first dose of the respective drug) and the exclusion of children who were already ventilated in the onasemnogene abeparvovec studies. More details can be found in dossier assessment A21-68 [1].

Regarding the aspect "disease duration", the company submitted additional analyses in the commenting procedure [4]. Regarding the aspect "exclusion of ventilated children", the company Biogen subsequently submitted information on nusinersen after the oral hearing [5]. Both aspects are assessed below.

2.1 Analyses subsequently submitted by the company on the aspect "disease duration"

With its comments, the company presented an updated comparison of individual arms on the outcomes "death" and "permanent ventilation" as well as on the composite outcome "death or permanent ventilation" [6]. For this comparison, it used a subpopulation of the studies STR1VE-EU and STR1VE-US for onasemnogene abeparvovec and a subgroup of the ENDEAR study for nusinersen. The aim of the company was to approximate the populations with regard to the characteristic "disease duration", as disease duration was notably shorter in the onasemnogene studies than in the nusinersen studies. In its data subsequently submitted, the company therefore used subpopulations with a disease duration of < 12 weeks from the 3 mentioned studies on both drugs.

The subpopulation formed by the company on onasemnogene abeparvovec comprised a total of 47 of the 54 children in the studies STR1VE-EU and STR1VE-US (87%). One death and no permanent ventilation had occurred in this subpopulation formed by the company, whereas a total of 3 events had occurred in the total population of the 2 studies (2 deaths, one permanent ventilation). The subpopulation of the ENDEAR study on nusinersen includes 34 of the 80 subjects (43%) and concurs with the subgroup of the ENDEAR study already presented in dossier assessment A21-68. Six events occurred in this subpopulation (3 deaths and 3 permanent ventilations) out of a total of 31 events in the total population (13 deaths, 18 permanent ventilations).

Two aspects in particular stand out in the company's analysis:

- The company did not consider the START study on onasemnogene abeparvovec. The START study comprises a total of 12 children who were treated in compliance with the

approval (cohort 2). According to the company, there were no data or, according to the subsequently submitted data after the oral hearing [4], only approximate values for delimiting the population, as the onset of symptoms had been only roughly recorded. For some of the children, however, the clinical study report (CSR) of the START study contains specific dates for the onset of symptoms, and there is also a reference to a database of the company on anamnestic information [7], so that this statement does not apply to at least some of the children. However, since there were no events of death or permanent ventilation under onasemnogene abeparvovec in cohort 2 of the START study, the non-consideration of the START study is not expected to produce a bias of the results in favour of onasemnogene abeparvovec.

- For the subgroup analysis on nusinersen, disease duration was operationalized as time from symptom onset to screening (instead of first dose) in the ENDEAR study. For this reason, the company did not use the time of the first dose as a criterion for onasemnogene abeparvovec either. This is understandable, but in contrast to the nusinersen study, it chose the parents' informed consent instead of the screening to determine disease duration, although information on the time point of screening is also available.

Given the small number of patients and events in both the onasemnogene abeparvovec studies and the nusinersen study, this unjustified deviation from the operationalization of the disease duration is potentially important. In contrast to the total population, no event of permanent ventilation occurred in the subpopulation formed by the company. According to the CSR of the STR1VE-US study, the latency period between symptom onset and first dose was 3.1 months, i.e. approx. 14 weeks, for the child who had permanent ventilation during the course of the study and who is therefore not included in the subpopulation of the company [8]. According to the data subsequently submitted by the company after the oral hearing, the consent forms in the STR1VE-US study were signed at a median of 2 weeks before the first dose [4]. A difference of only a few days between screening and informed consent could therefore be decisive for or against the inclusion of this child in the subpopulation with disease duration of < 12 weeks if the time point of screening had been used instead of the informed consent. Because of a lack of corresponding information in the CSR, it is unclear whether this also applies to the child who died in the STR1VE-EU study, who is also not included in the subpopulation of the company.

Irrespective of the question of the suitability of the subpopulation formed by the company, the analyses subsequently submitted by the company are also not complete. For example, there are no analyses of the outcome "motor milestone achievement", although disease duration was a relevant effect modifier in the ENDEAR study also for this outcome. This was also described in dossier assessment A21-68 [1].

2.2 Information on nusinersen subsequently submitted by company Biogen (study ENDEAR)

Dossier assessment A21-68 described that there were important differences between the studies on onasemnogene abeparvovec and nusinersen regarding the inclusion or exclusion of children

who were already ventilated because, in contrast to the nusinersen studies, these children were excluded from the onasemnogene abeparvovec studies [1]. This was confirmed by the company in the oral hearing [2].

In order to assess whether the less strict exclusion criteria of the nusinersen studies could have a relevant influence on the result, the company Biogen was therefore asked to submit further information on nusinersen. Specifically, the question was to be answered whether those children in the subgroup of the ENDEAR study described in Section 2.1 who had an event (death [n = 3] or permanent ventilation [n = 3]) had already been ventilated before the start of the study.

According to the company Biogen, none of the 3 children who died were already ventilated at the start of the study [5]. Of the 3 children for whom an event of permanent ventilation was registered, one child had already been ventilated at the start of the study and one child had not been ventilated. This remained unclear for the third child, as baseline data (day 1) were missing for this child. However, data were available from day 2 of the study showing that the child was being ventilated at this time, so that there is a high probability that the child was also ventilated at baseline.

Overall, the data show that the extended inclusion criteria of the nusinersen studies may cause potential bias of the result to the disadvantage of nusinersen.

2.3 **Summary**

The analyses of the subpopulation with disease duration of < 12 weeks subsequently submitted by the company on onasemnogene abeparvovec are unsuitable for the derivation of the added benefit and are incomplete. Therefore, no relevant gain in knowledge results from these analyses compared with dossier assessment A21-68.

Furthermore, the subsequently submitted data of the company Biogen show that at least one, possibly 2, of the 3 events of permanent ventilation in the ENDEAR study occurred in children with pre-existing ventilation. This supports the argument of insufficient similarity of the study populations because of different exclusion criteria.

For an adequate analysis, it would be useful to form a subpopulation of children with disease duration < 12 weeks, excluding children ventilated at baseline, from both nusinersen studies (ENDEAR and CS3A). A comparison of all relevant outcomes could then be conducted between this subpopulation and a subpopulation of the 3 onasemnogene abeparvovec studies formed using the same criteria.

Overall, the overall consideration of the analyses subsequently submitted with the comments results in no hint of an added benefit of onasemnogene abeparvovec in comparison with the ACT nusinersen in patients with SMA type 1. Thus, the data do not change the conclusion on the added benefit of onasemnogene abeparvovec from dossier assessment A21-68.

The following Table 1 shows the result of the benefit assessment of onasemnogene abeparvovec under consideration of dossier assessment A21-68 and the present addendum.

Table 1: Onasemnogene abeparvovec – extent and probability of added benefit

Research question	**Subindication**	**ACT[a]**	**Extent and probability of added benefit**
	Patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene with		
1	SMA type 1	Nusinersen	Added benefit not proven
2	SMA type 2		Added benefit not proven
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[b]	Added benefit not proven
4	Pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene	Nusinersen	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Various measures, including e.g. physiotherapy according to the catalogue of remedies (catalogue of prescribable remedies according to §92 (6) SGB V as the second part of the guideline on the prescription of remedies in contracted doctor care [9]), may be suitable in this therapeutic indication for treating the patient's individual symptoms of SMA or a corresponding ventilation of the patient, if necessary.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SGB: Social Code Book; SMA: spinal muscular atrophy; SMN: survival motor neuron

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Onasemnogen-Abeparvovec (spinale Muskelatrophie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 17.08.2021]. URL: https://www.iqwig.de/download/a21-68_onasemnogen-abeparvovec_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses; hier: Onasemnogen-Abeparvovec (D-679) [online]. 2021 [Accessed: 12.10.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/689/#stellungnahmen.

3. Novartis Gene Therapies. Onasemnogen-Abeparvovec (ZOLGENSMA); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 25.08.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/689/#dossier.

4. Novartis Gene Therapies. Onasemnogen-Abeparvovec (ZOLGENSMA): zusätzliche Analysen; Nachreichung von Auswertungen nach der mündlichen Anhörung [unpublished]. 2021.

5. Biogen GmbH. Nusinersen (Spinraza): zusätzliche Analysen; Nachreichung von Auswertungen nach der mündlichen Anhörung [unpublished]. 2021.

6. Novartis Gene Therapies. Stellungnahme zum IQWiG-Bericht Nr. 1177: Onasemnogen-Abeparvovec (spinale Muskelatrophie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A21-68. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/689/#beschluesse in the document "Zusammenfassende Dokumentation"].

7. Novartis Gene Therapies. AVXS-101, Protocol AVXS-101-CL-101, Phase I Gene Transfer Clinical Trial for Muscular Atrophy Type 1 Dellivering AVXS-101; study AVXS-101-CL-101; clinical study report [unpublished]. 2018.

8. Novartis Gene Therapies. AVXS-101, AVXS-101-CL-103, Phase 3, Open-label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with one or two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion; study AVXS-101-CL-103; clinical study report [unpublished]. 2020.

9. Gemeinsamer Bundesausschuss. Heilmittel-Richtlinie - Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung (HeilM-RL) [online]. 2021 [Accessed: 01.07.2021]. URL: https://www.g-ba.de/downloads/62-492-2324/HeilM-RL_2020-10-15_iK-2021-01-01.pdf.

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