IQWiG Reports – Commission No. A21-43

Nusinersen (spinal muscular atrophy) – Addendum to Commission A20-114[1]

Addendum

Commission: A21-43
Version: 1.0
Status: 30 April 2021

[1] Translation of addendum A21-43 *Nusinersen (spinale Muskelatrophie) – Addendum zum Auftrag A20-114* (Version 1.0; Status: 30 April 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Nusinersen (spinal muscular atrophy) – Addendum to Commission A20-114

Commissioning agency
Federal Joint Committee

Commission awarded on
8 April 2021

Internal Commission No.
A21-43

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Sascha Abbas
- Virginia Seiffart
- Lars Beckmann
- Sibylle Sturz
- Beate Wieseler

Keywords: Nusinersen, Muscular Atrophy – Spinal, Benefit Assessment, NCT02193074, NCT02292537, NCT02386553, NCT02462759, NCT02594124

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CHOP INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Examination
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RULM	Revised Upper Limb Module
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SPC	Summary of Product Characteristics

1 Background

On 8 April 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-114 (Nusinersen – Benefit assessment according to §35a Social Code Book V) [1].

In Module 4 A.1 of its dossier on nusinersen [2], the pharmaceutical company (hereinafter referred to as "the company") presented the randomized controlled trial (RCT) ENDEAR [3-7] for patients with 5q spinal muscular atrophy (SMA) and early onset of disease (SMA type 1, research question 1). The study was used for the benefit assessment of nusinersen [1]. For patients with 5q SMA and later onset of disease (SMA type 2, research question 2), the company presented the RCT CHERISH [8-10]. The CHERISH study was not included in the benefit assessment due to the lack of evidence of an adequate implementation of best supportive care (BSC) in accordance with the health care standard in Germany. The results of the study were presented as supplementary information in the appendix of the benefit assessment [1].

For pre-symptomatic patients with 5q SMA (research question 3), the company presented results of the single-arm NURTURE study with nusinersen in pre-symptomatic patients with 5q SMA [11-13] in Module 4 A.3 of its dossier [2]. The single-arm NURTURE study was not suitable for the assessment of the added benefit of nusinersen in comparison with the appropriate comparator therapy (ACT). In the context of the dossier assessment, an added benefit was derived for pre-symptomatic patients limited to 2 survival motor neuron (SMN)2 gene copies by transferring the evidence from the ENDEAR study in patients with early onset of disease [1].

To be able to decide on the added benefit, the G-BA needs further analyses in this procedure. The G-BA therefore commissioned IQWiG with the following assessment of the analyses submitted by the company under consideration of the information provided in the dossier:

- results of the patient group of the SHINE study, in which patients from the CHERISH study were enrolled (long term SHINE-CHERISH data)
- results of the NURTURE study for patients with 3 SMN2 gene copies
- mean differences for the outcome "Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND)" (study ENDEAR)
- outcome "hospitalizations" (study ENDEAR and CHERISH)

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

The individual aspects commissioned by the G-BA are examined in the following sections. The assessment is divided as follows:

- Section 2.1: assessment of the outcomes "hospitalizations" and "motor functioning" (assessed by CHOP INTEND) for research question 1 (patients with early onset of disease [infantile form, SMA type 1])
- Section 2.2: assessment of the outcome "hospitalizations" and of the results of the patient group of the SHINE study, which included patients from the CHERISH study (long-term SHINE-CHERISH data) for research question 2 (patients with later onset of disease [SMA type 2])
- Section 2.3: assessment of the results of the NURTURE study for patients with 3 SMN2 gene copies for research question 3 (pre-symptomatic patients)

2.1 Research question 1: patients with early onset of disease (SMA type 1)

The benefit assessment used the ENDEAR study for the assessment of the added benefit of nusinersen in comparison with the ACT BSC in patients with early onset of disease (SMA type 1, research question 1). The study is a double-blind, randomized trial that included patients with genetic documentation of 5q SMA, 2 SMN2 gene copies and ≤ 7 months of age at study start as well as symptom onset at ≤ 6 months of age. The design of the study as well as the characteristics of the interventions and the study populations are presented in benefit assessment A20-114 [1].

The present addendum assesses the results presented by the company in Module 4 A.1 [2] for the ENDEAR study for the outcomes "hospitalizations" and "motor functioning" assessed by CHOP INTEND.

2.1.1 Assessment of the outcome "hospitalizations"

For the outcome "hospitalizations", the company presented analyses of the frequency of hospitalizations (rate ratio) and the time to hospitalization in its dossier [2]. The frequency of hospitalizations due to the following reasons was recorded: "monitoring for general observation", symptoms after "dosing or sham intervention under BSC", "serious adverse events (SAEs)" or "additional investigations" (e.g. planned surgery). "Monitoring for general observation" included treatments not related to the study medication or sham intervention under BSC or due to adverse events (AEs) or SAEs. "Dosing or sham intervention under BSC" included treatments for safety reasons (not for specific reasons such as AEs or SAEs). "SAEs" included treatments due to an SAE. "Additional investigations" included planned treatments (e.g. placement of a gastric feeding tube for preventive reasons and not due to an AE). The recording of the outcome "hospitalization" as well as the analysis of the frequency were predefined.

The outcome “hospitalizations” was not used in the benefit assessment of nusinersen because, according to the operationalization, it could also include events such as planned surgery or monitoring for general observation, which do not have to be associated with the disease.

Results of the outcome “hospitalizations”

Irrespective of the relevance of the outcome “hospitalizations” for the benefit assessment of nusinersen, the results on the frequency of hospitalizations (rate ratio) are presented in Appendix A, Table 6. These results show no statistically significant difference between nusinersen + BSC in comparison with sham intervention + BSC.

2.1.2 Assessment of the outcome “motor functioning” (assessed by CHOP INTEND)

For motor function, the company presented results for the Hammersmith Infant Neurological Examination (HINE) Section 2 and for the CHOP INTEND in its dossier. For the outcome “motor milestone achievement”, the results of the responder analyses of the HINE Section 2 were used for the benefit assessment of nusinersen, as particularly motor development with regard to motor milestone achievement is an important therapeutic goal in the present therapeutic indication, and these are represented by HINE Section 2. In addition, the presented response criterion is face valid. The CHOP INTEND, on the other hand, represents motor functioning. Although the results of the mean differences of the CHOP INTEND were not presented in the benefit assessment of nusinersen, it was described that the results pointed in the same direction as the used results of the HINE Section 2 [1]. The G-BA commissioned IQWiG with the assessment of the results of the mean differences of the CHOP INTEND presented by the company.

The CHOP INTEND is a validated instrument for the assessment of motor functioning [14,15]. It was developed for SMA type 1 patients and consists of 16 items, each rated with a score from 0 (non-functional) to 4 (fully functional). This results in a total score of 0 to 64 points, with higher scores corresponding to better motor functioning. The results of the analyses presented by the company for the mean differences of the CHOP INTEND are used for the assessment of motor functioning in patients with type 1 SMA in addition to the results on the HINE Section 2 presented in dossier assessment A20-114 [1] for the assessment of the added benefit and assessed together (see Section 2.1.3).

Risk of bias

The results of the outcome “motor functioning” assessed by CHOP INTEND have a high risk of bias due to the high proportion of missing values at baseline (difference > 10%), which differed between the treatment arms. The high proportion of missing values in the course of the study, which differed between the arms, was due to the early discontinuation of the ENDEAR study due to the early proof of efficacy of nusinersen.

Results

The results of the mean differences for the outcome "motor functioning" assessed by CHOP INTEND are presented in Table 1.

Table 1: Results (morbidity), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. placebo + BSC, patients with early onset of disease (SMA type 1)

Study Outcome category	Nusinersen + BSC			Placebo + BSC			Nusinersen + BSC vs. placebo + BSC
Outcome Time point	N[a]	Values at baseline mean (SD)	Change at time point mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at time point mean[b] (SE)	MD [95% CI]; p-value[b]
ENDEAR							
Morbidity							
Motor functioning (CHOP INTEND)[c]							
Day 64	73	27.3 (7.9)	3.97 (0.87)	33	29.0 (7.9)	−3.02 (1.32)	6.98 [3.79; 1.02]; < 0.001 Hedges' g 1.04 [0.60; 1.47]
Day 183	59	27.3 (7.9)	8.92 (1.09)	23	29.0 (7.9)	−10.29 (1.80)	1.92 [1.49; 2.35]; < 0.001 Hedges' g 2.28 [1.68; 2.88]
Day 302	36	27.3 (7.9)	10.89 (1.43)	16	29.0 (7.9)	−9.71 (2.21)	2.06 [1.51; 2.61]; < 0.001 Hedges' g 2.55 [1.77; 3.33]
Day 394	26	27.3 (7.9)	13.55 (1.59)	11	29.0 (7.9)	−10.90 (2.53)	2.45 [1.82; 3.07]; < 0.001 Hedges' g: 2.91 [1.92; 3.91]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Linear models with the covariates disease duration at screening and age at symptom onset.
c. Higher (increasing) values indicate better symptoms; positive effects (intervention minus control) indicate an advantage for the intervention.

BSC: best supportive care; CHOP INTEND: Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease; CI: confidence interval; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMA: spinal muscular atrophy; vs.: versus

The certainty of conclusions of the results of the outcome "motor functioning" measured by the CHOP INTEND is reduced due to the high risk of bias (see above). However, the certainty of conclusions of the results is not downgraded despite this risk of bias because of the effect sizes in the course of the study (see below). Hence, at most indications, e.g. of an added benefit, can be determined for this outcome.

For the outcome "motor functioning" measured by the CHOP INTEND, there was a statistically significant difference in favour of nusinersen + BSC compared with sham intervention + BSC

at all time points of measurement during the study (day 64, day 183, day 302 and day 394). Since the confidence interval of Hedges' g is fully outside the irrelevance range [−0.2; 0.2] at all time points, this is interpreted to be a relevant effect. There is a high risk of bias for this outcome due to the high proportion of missing values at baseline. The observed effect became larger in the course of the study, with the extent, as measured by the confidence interval, also becoming larger, despite increasing uncertainty due to the early end of the study and the associated missing values. Thus, it is not assumed that the effect and the extent of the effect were caused by systematic bias alone. Overall, there is therefore an indication of an added benefit of nusinersen + BSC in comparison with sham intervention + BSC for the outcome "motor functioning" measured by the CHOP INTEND.

Subgroups and other effect modifiers

Based on the mean differences, no relevant effect modification by sex (male/female) or disease severity (age at symptom onset ≤ 12 weeks/> 12 weeks) was identified for the outcome "motor functioning" measured by the CHOP INTEND. For the subgroup characteristic of disease duration (≤ 12 weeks/> 12 weeks), there was a statistically significant effect modification at days 64, 183 and 302. The effects in both subgroups were statistically significant and relevant at day 183 and day 302. A difference between the subgroups according to disease duration only existed at day 64: There was a statistically significant and relevant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC for patients with a disease duration of ≤ 12 weeks; there was also a statistically significant difference between the groups for patients with a disease duration of > 12 weeks. Since the confidence interval of Hedges' g is not fully outside the irrelevance range [−0.2; 0.2], this is not interpreted to be a relevant effect. As this difference between the subgroups according to disease duration did not persist after day 64 in the course of the study, it is not considered further.

2.1.3 Probability and extent of added benefit

Determination of the outcome category for the outcome "motor functioning" measured by the CHOP INTEND

The outcome "motor functioning", measured by the CHOP INTEND, was assigned to the outcome category of serious/severe symptoms/late complications. This is due to the fact that the patient population with early-onset SMA (SMA type 1) comprised by research question 1 generally have severe impairments regarding motor functioning. This is shown by the fact that, contrary to normal motor development for their age, the patients included in the study had limited motor functioning at baseline (mean values of the CHOP INTEND at baseline: 27.3 in the nusinersen arm versus 29.0 in the BSC arm) [16].

Assessment of the added benefit at outcome level for the CHOP INTEND

Overall, there was an indication of an added benefit of nusinersen + BSC in comparison with sham intervention + BSC for the outcome "motor functioning" measured by the CHOP INTEND. The extent of the effect is non-quantifiable.

Overall conclusion on added benefit

For the assessment of motor function (outcome category of morbidity) of patients with early symptom onset (SMA type 1), results are available for the outcomes "motor functioning" measured by the CHOP INTEND and "motor milestone achievement" measured by HINE Section 2. The results of both outcomes were considered together for the derivation of the added benefit. This resulted in an indication of major added benefit of nusinersen in comparison with BSC for the outcome "motor milestone achievement" measured by HINE Section 2 for patients with a disease duration of ≤ 12 weeks (see A20-114 [1]). For the outcome "motor functioning" measured by the CHOP INTEND, there was an indication of an added benefit independent of the duration of the disease. The extent of this effect is non-quantifiable, but, due to the size of the effect, supports the results of the outcome "motor milestone achievement" measured by HINE Section 2 in the group of patients with short disease duration. Overall, there was therefore an indication of a major added benefit of nusinersen in comparison with BSC for motor function for patients with a short disease duration of ≤ 12 weeks. For patients with a disease duration of > 12 weeks, there was a non-quantifiable added benefit of nusinersen in comparison with BSC.

In the overall view of all outcomes, the additional consideration of the outcome "motor functioning" measured by the CHOP INTEND has not changed the conclusion on the added benefit of nusinersen from dossier assessment A20-114.

2.2 Research question 2: patients with later onset of disease (SMA type 2)

For the assessment of the added benefit of nusinersen in comparison with the ACT BSC in patients with later onset of disease (SMA type 2, research question 2), the RCT CHERISH presented by the company in Module 4 A.2 [2] was not included in the benefit assessment due to the lack of evidence of an adequate implementation of BSC in accordance with the health care standard in Germany. The study characteristics and the results of the study were presented as supplementary information in the appendix of dossier assessment A20-114 [1].

Patients who had participated in the CHERISH study had the option to participate in the open-label long-term SHINE study [17,18] after the last study visit. The company presented the data from the SHINE study in Module 4 A.4 for the comparison of early versus late nusinersen administration [2]. This analysis of the SHINE study was not taken into account for the benefit assessment of nusinersen, as no conclusions on the added benefit of nusinersen in comparison with the ACT BSC can be derived from the results. Besides, due to the lack of relevance of the CHERISH study for the benefit assessment of nusinersen, the results of the SHINE-CHERISH study were not considered for the assessment of the long-term efficacy of nusinersen. A description of the SHINE study can be found in dossier assessment A20-114 [1].

The present addendum assesses the results presented by the company in Module 4 A.2 for the CHERISH study for the outcome "disease-related hospitalizations" based on SAEs. It also assesses the results of the patient group of the SHINE study, in which patients from the CHERISH study were enrolled (long-term SHINE-CHERISH data) for research question 2.

In addition to the assessment commissioned by the G-BA, the results of the specific AEs "vomiting", "headache" and "back pain" of the CHERISH study are presented.

2.2.1 Assessment of the outcome "disease-related hospitalizations" based on SAEs

Disease-related hospitalizations were defined as SAEs that required inpatient hospitalization or where hospitalization was prolonged. The classification of an SAE as disease-related hospitalization was made by a blinded committee. The operationalization of the outcome is considered useful to reflect disease-related hospitalizations.

For the outcome "disease-related hospitalizations" based on SAEs, the company presented analyses on the frequency of these hospitalizations (rate ratio) and the time to event in Module 4 A.2 [2]. The recording of the outcome "disease-related hospitalizations" as well as the analysis of the frequency were predefined.

Results of the outcome "disease-related hospitalizations"

Irrespective of the relevance of the CHERISH study for the benefit assessment of nusinersen, the results on the frequency of disease-related hospitalizations based on SAEs (rate ratio) are presented in Appendix B.1, Table 7. These results show a statistically significant difference in favour of nusinersen. It should be noted that the observed effect in favour of nusinersen was largely due to the serious respiratory events included in this outcome (11 events in 84 patients in the nusinersen arm, 14 events in 42 patients in the sham intervention arm). The results for the outcome "serious respiratory events" were presented in the appendix of dossier assessment A20-114 [1]. They showed no difference in favour or to the disadvantage of nusinersen.

2.2.2 Assessment of the specific AE outcomes "vomiting", "headache" and "back pain"

The specific AE outcomes "vomiting", "headache" and "back pain" were identified on the basis of the common AEs and SAEs that occurred in the CHERISH study and their differences between the treatment arms, and taking into account patient relevance. These outcomes were not presented in benefit assessment A20-114 because the CHERISH study was not included in the benefit assessment.

Results of the outcomes "vomiting", "headache" and "back pain"

Irrespective of the relevance of the CHERISH study for the benefit assessment of nusinersen, the results on the specific AE outcomes "vomiting", "headache" and "back pain" are presented in Appendix B.1, Table 7. They show a statistically significant difference to the disadvantage of nusinersen for all 3 outcomes.

2.2.3 Assessment of the results of the SHINE-CHERISH study

Hereinafter, only the group of the SHINE study, in which patients from the CHERISH study were included (hereinafter referred to as "SHINE-CHERISH"), is considered. All patients, except one, who had completed the CHERISH study transitioned to the SHINE-CHERISH study (42 children treated with a sham intervention in the CHERISH study [group 2 A] and

83 children treated with nusinersen in the CHERISH study [group 2 B]). The design of the study included a blinded loading phase (injections on days 1, 29 and 85), after which patients from both groups received unblinded nusinersen as a maintenance dose every 4 months. However, deviating from the Summary of Product Characteristics (SPC), which specifies treatment with 4 loading doses (days 0, 14, 28 and 63), patients in the SHINE-CHERISH study were treated with nusinersen on study days 1, 29 and 85 (loading) [19]. Day 0 in the SPC corresponds to day 1 in the study. The study is ongoing with a planned study duration of 5 years (from day 1 of the maintenance dose to day 1800) and a planned end of study in 2023.

Results of the SHINE-CHERISH study

Irrespective of the relevance of the studies CHERISH and SHINE-CHERISH for the benefit assessment of nusinersen, the results of the open-label long-term SHINE-CHERISH study are presented as supplementary information in Appendix B.2 to assess the long-term efficacy of nusinersen. The results show that the improvement in the morbidity outcomes "Hammersmith Functional Motor Scale Expanded (HFMSE)" and "Revised Upper Limb Module (RULM)" was sustained until day 1410 (approximately 3.5 years). No conclusion can be drawn regarding a longer period of time due to the low patient numbers at the later documentation time points. No conclusion can be drawn regarding long-term safety of nusinersen on the basis of the results of the SHINE-CHERISH study, as all patients were treated with nusinersen.

2.3 Research question 3: pre-symptomatic patients

2.3.1 Assessment of the results of the NURTURE study for patients with 3 SMN2 gene copies

Dossier assessment A20-114 derived an added benefit from the transfer of the results of the subpopulation of patients with early symptomatic start of therapy (disease duration ≤ 12 weeks) from the ENDEAR study to pre-symptomatic patients (limited to those with 2 SMN2 gene copies) [1]. The approach of transferring evidence was used under the assumption that pre-symptomatic patients with 2 SMN2 gene copies from the NURTURE study develop an early onset of disease in the natural course of the disease, i.e. SMA type 1, corresponding to the patients in the ENDEAR study, and that therefore basic comparability between the patient populations used could be assumed. In addition, an approximation of the 2 patient populations was achieved by limiting the maximum disease duration, i.e. the period between disease onset and start of therapy, to 12 weeks in the ENDEAR study. A transfer of evidence from the ENDEAR study to pre-symptomatic patients with 2 SMN2 gene copies was possible, as the comparison of results consistently showed better results of a pre-symptomatic start of therapy with nusinersen compared with an early symptomatic start of therapy across all considered benefit outcomes [1].

In the framework of the commenting procedure, the G-BA commissioned IQWiG to assess the results of the NURTURE study for pre-symptomatic patients with 3 SMN2 gene copies. As already explained in the dossier assessment, the single-arm NURTURE study is not suitable for the assessment of the added benefit of nusinersen in comparison with the ACT [1]. In the

following, it is therefore examined whether it is possible to use an approach for the derivation of the added benefit in pre-symptomatic patients with 3 SMN2 gene copies analogous to the approach used for patients with 2 SMN2 gene copies in dossier assessment A20-114. It is examined whether the evidence from the CHERISH study comparing nusinersen against sham intervention in patients with later onset of disease (SMA type 2) and 2 to 4 SMN2 gene copies can be transferred to pre-symptomatic patients with 3 SMN2 gene copies.

Analyses including patient characteristics for the subpopulation of patients with 3 SMN2 gene copies are not available in the CHERISH study. However, since 88% of the patients in the CHERISH study had 3 SMN2 gene copies, the entire study population of the CHERISH study can be used as an approximation. In the CHERISH study, the disease duration in terciles (< 25, ≥ 25 to < 44, ≥ 44 months) was prespecified as a subgroup characteristic. Irrespective of the meaningfulness of this classification, an effect modification for the subgroup characteristic of disease duration was shown for the patient-relevant morbidity outcomes "HFMSE" and "RULM" on day 456 (last available documentation time point). In the subgroup with < 25 months of disease duration, advantages for nusinersen over the sham intervention were shown for both outcomes. Since the subpopulation with the shortest disease duration is also more suitable for a comparison with pre-symptomatic patients, the subpopulation with < 25 months of disease duration of the CHERISH study is considered below.

To assess the comparability of the patient populations, the patient characteristics of the patients with 3 SMN2 gene copies in the nusinersen arms of the NURTURE study are first compared with those of the CHERISH study (see Table 2). No characteristics are available for patients with a disease duration of < 25 months.

Table 2: Characteristics of the study populations – comparison: nusinersen, NURTURE study (pre-symptomatic, 3 SMN2 gene copies) versus nusinersen, CHERISH study (later onset of disease, SMA type 2)

Characteristic	**Nusinersen study NURTURE (pre-symptomatic, 3 SMN2 gene copies) N = 10**	**Nusinersen study CHERISH[a] N = 84**
Sex [F/M], %	60/40	55/45
Age at first dose (NURTURE) or screening (CHERISH), median [Q1; Q3]	23 [12; 25] days	4 [2; 5] years
Age at symptom onset [months], median [Q1; Q3]	Not applicable	10 [9; 13]
Disease duration [months], median [Q1; Q3]	Not applicable	39 [24; 51]
Age at diagnosis [months], median [Q1; Q3]	ND	18 [16; 22]
Time since diagnosis [months], median [Q1; Q3]		28 [17; 40]

a. In the CHERISH study, 74 out of 84 (88%) of all patients randomized to the nusinersen arm had 3 SMN2 gene copies.

F: female; M: male; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; SMA: spinal muscular atrophy; SMN: survival motor neuron

As expected, pre-symptomatic patients were notably younger at diagnosis than patients with later onset of disease (< 23 days in the NURTURE study versus a median of 18 months in the CHERISH study). While pre-symptomatic patients started therapy immediately after diagnosis, patients with a later onset of disease had a median age of 4 years when they started therapy. Thus, patients in the CHERISH study were only treated after a median disease duration of 39 months.

Due to the different starting situations of the patients in the 2 studies NURTURE (pre-symptomatic) and CHERISH (later onset of disease), it can be assumed that a transfer of evidence, analogous to the approach in early symptomatic patients from the ENDEAR study, from the CHERISH study to pre-symptomatic patients with 3 SMN2 gene copies is not meaningfully possible. Restricting the study population of the CHERISH study to a disease duration of < 25 months also does not lead to a better comparability of the 2 patient populations. The fact that a comparison of the results of the studies CHERISH and NURTURE to check the transfer of evidence is not possible in a meaningful way is also shown by the fact that the outcomes recorded in the CHERISH study for patients with a later onset of disease were not recorded in the NURTURE study (RULM) or were only recorded for patients who were > 2 years old at the documentation time points (HFMSE) (see Table 4).

In accordance with the G-BA's commission, the results of the NURTURE study for patients with 3 SMN2 gene copies are presented below. These results are compared with the results of the CHERISH study for patients with a disease duration of < 25 months. In addition to the outcomes of mortality and side effects, only the patient-relevant outcomes of the outcome category of morbidity are presented, which showed statistically significant differences between the treatment groups also in the CHERISH study.

Table 3: Results (morbidity, mortality, side effects) – comparison: nusinersen, NURTURE study (pre-symptomatic, 3 SMN2 gene copies) versus nusinersen, CHERISH study (later onset of disease, SMA type 2, disease duration < 25 months)

Outcome category **Outcome**	**Nusinersen study NURTURE[a] (pre-symptomatic, 3 SMN2 gene copies)**		**Nusinersen study CHERISH[b] (disease duration < 25 months)**	
	N[c]	**Adjusted annual rate [95% CI]** **Number of events**	**N[c]**	**Adjusted annual rate [95% CI][d]** **Number of events**
Morbidity				
Disease-related hospitalizations based on SAEs[e]	10	ND ND[f]	24	0.01 (0.00; NA) 1
	N[c]	**Patients with event n (%)**	**N[c]**	**Patients with event n (%)**
Mortality				
Overall survival	10	0 (0)	24	0 (0)
Side effects				
SAEs		No usable data[g]		
Discontinuation due to AEs		No usable data[g]		
Vomiting (PT, AE)	10	1 (10)	24	7 (29.2)
Headache (PT, AE)	10	No usable data[h]	24	4 (16.7)
Back pain (PT, AE)	10		24	4 (16.7)

a. Data cut-off of the NURTURE study: 15 May 2018.
b. In the CHERISH study, 74 out of 84 (88%) of all patients randomized to the nusinersen arm had 3 SMN2 gene copies.
c. Number of patients in the analysis.
d. Negative binomial regression with treatment and age after study start as independent variables.
e. SAEs that required inpatient hospitalization or where hospitalization was prolonged; disease-related hospitalization was classified by a blinded committee.
f. A total of 2 SAEs occurred in patients with 3 SMN2 gene copies.
g. High proportion of events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. SOC "respiratory, thoracic and mediastinal disorders").
h. Patients with 3 SMN2 gene copies were 6 weeks of age or younger at the first dose of the study medication and were observed for a median [Q1; Q3] of 23 [19; 30] months at the 15 May 2018 data cut-off. Thus, recording the AEs "headache" and "back pain" is not possible for children of this age.

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; PT: Preferred Term; Q1: first quartile; Q3: third quartile; SAE: serious adverse event; SMA: spinal muscular atrophy; SMN: survival motor neuron; SOC: System Organ Class

Table 4: Results (morbidity, continuous) – comparison: nusinersen, NURTURE study (pre-symptomatic, 3 SMN2 gene copies) versus nusinersen, CHERISH study (later onset of disease, SMA type 2, disease duration < 25 months)

Outcome category Outcome	Nusinersen study NURTURE[a] (pre-symptomatic, 3 SMN2 gene copies)			Nusinersen study CHERISH[b] (disease duration < 25 months)		
	N[c]	Values at baseline mean (SD)	Change mean (SE)	N[c]	Values at baseline mean (SD)	Change at day 456 mean[d] (SE)
Morbidity						
Motor milestone achievement (HFSME)[e]	10	ND[f]		20	ND	7.3 (1.2)
RULM[e]		Not recorded		20	ND	7.6 (0.9)

a. Data cut-off of the NURTURE study: 15 May 2018.
b. In the CHERISH study, 74 out of 84 (88%) of all patients randomized to the nusinersen arm had 3 SMN2 gene copies.
c. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline (possibly at other time points) may be based on other patient numbers.
d. Adjusted mean changes were calculated using linear models with treatment (sham intervention, nusinersen) as fixed effect and adjusted for age at baseline and value at baseline. In case of missing values, multiple imputation was performed using ANCOVA with treatment (sham intervention, nusinersen) as fixed effect and the covariates age at baseline and value at baseline.
e. Higher (increasing) values mean better motor function.
f. According to information provided by the company in Module 4 A.3 of the dossier, the HFMSE was only recorded in patients who were > 2 years old at the documentation time and who had a CHOP INTEND score of ≥ 50 at 2 consecutive study visits. According to the company, data for the time points of day 778 or day 897 were available for a total of 10 of the 25 included patients. The total score for these patients was between 11 and 48 points.

ANCOVA: analysis of covariance; HFMSE: Hammersmith Functional Motor Scale Expanded; N: number of analysed patients; ND: no data; RULM: Revised Upper Limb Module; SD: standard deviation; SE: standard error; SMA: spinal muscular atrophy; SMN: survival motor neuron

2.3.2 Probability and extent of added benefit

Based on the data from the studies CHERISH and NURTURE, it is not possible to transfer evidence from the CHERISH study to pre-symptomatic patients with 3 SMN2 gene copies. Thus, an added benefit of nusinersen for pre-symptomatic patients with 3 SMN2 gene copies is not proven. The conclusion on the added benefit of nusinersen for research question 3 from dossier assessment A20-114 is therefore not changed.

2.4 Summary

The data subsequently assessed in the present addendum have not changed the conclusion on the added benefit of nusinersen from dossier assessment A20-114.

The following Table 5 shows the result of the benefit assessment of nusinersen under consideration of dossier assessment A20-114 and the present addendum.

Table 5: Nusinersen – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with 5q SMA and early onset of disease (infantile form, SMA type 1)	BSC[b]	Indication of major added benefit[c]
Patients with 5q SMA and later onset of disease (SMA type 2, type 3 and type 4)		Added benefit not proven
Pre-symptomatic patients with 5q SMA		Hint of a non-quantifiable added benefit[d]

a. Presentation of the 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 [20]), 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. In addition, it is assumed that BSC is implemented in both study arms. In patients with pre-symptomatic SMA, BSC also includes watchful waiting.
c. Only patients with 2 SMN2 gene copies were included in the ENDEAR study. It remains unclear whether the observed effects can be transferred to patients with another number of SMN2 gene copies.
d. For patients with 2 SMN2 gene copies. No suitable data are available for patients with a different number of SMN2 gene copies.

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

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nusinersen (spinale Muskelatrophie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 01.03.2021]. URL: https://www.iqwig.de/download/a20-114_nusinersen_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Biogen. Nusinersen (Spinraza); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2020 [Accessed: 16.03.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/625/#dossier.

3. Biogen. A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy [online]. 2017 [Accessed: 22.01.2021]. URL: https://ClinicalTrials.gov/show/NCT02193074.

4. Finkel RS, Mercuri E, Darras BT et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017; 377(18): 1723-1732. https://dx.doi.org/10.1056/NEJMoa1702752.

5. Isis Pharmaceuticals. Eine randomisierte, doppelblinde, scheinbehandlungskontrollierte Phase-3-Studie zur Beurteilung der klinischen Wirksamkeit und Sicherheit von intrathekal verabreichtem ISIS 396443 bei Patienten mit infantiler spinaler Muskelatrophie [online]. [Accessed: 25.01.2021]. URL: http://www.drks.de/DRKS00009141.

6. Isis Pharmaceuticals. A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Infantile-onset Spinal Mus [online]. [Accessed: 25.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-004422-29.

7. Pane M, Coratti G, Sansone VA et al. Nusinersen in type 1 spinal muscular atrophy: Twelve-month real-world data. Ann Neurol 2019; 86(3): 443-451. https://dx.doi.org/10.1002/ana.25533.

8. Biogen. A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA) (CHERISH) [online]. 2018 [Accessed: 22.01.2021]. URL: https://ClinicalTrials.gov/show/NCT02292537.

9. Ionis Pharmaceuticals. A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Later-onset Spinal Muscular Atrophy [online]. [Accessed: 25.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001947-18.

10. Mercuri E, Darras BT, Chiriboga CA et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med 2018; 378(7): 625-635. https://dx.doi.org/10.1056/NEJMoa1710504.

11. Biogen Idec Research. An Open-Label Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects With Genetically Diagnosed and Presymptom [online]. [Accessed: 25.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-002098-12.

12. De Vivo DC, Bertini E, Swoboda KJ et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord 2019; 29(11): 842-856. https://dx.doi.org/10.1016/j.nmd.2019.09.007.

13. Biogen. A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy [online]. 2019 [Accessed: 25.01.2021]. URL: https://ClinicalTrials.gov/show/NCT02386553.

14. Glanzman AM, Mazzone E, Main M et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord 2010; 20(3): 155-161. https://dx.doi.org/10.1016/j.nmd.2009.11.014.

15. Glanzman AM, McDermott MP, Montes J et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther 2011; 23(4): 322-326. https://dx.doi.org/10.1097/PEP.0b013e3182351f04.

16. Kolb SJ, Coffey CS, Yankey JW et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. Ann Clin Transl Neurol 2016; 3(2): 132-145. https://dx.doi.org/10.1002/acn3.283.

17. Biogen. A Study for Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies [online]. 2020 [Accessed: 25.01.2021]. URL: https://ClinicalTrials.gov/show/NCT02594124.

18. Biogen Idec Research. An Open-label Extension Study for Patients with Spinal Muscular Atrophy who Previously Participated in Investigational Studies of ISIS 396443 [online]. [Accessed: 25.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-001870-16.

19. Biogen. Spinraza 12 mg Injektionslösung: Fachinformation [online]. 2019 [Accessed: 26.01.2021]. URL: https://www.fachinfo.de.

20. Gemeinsamer Bundesausschuss. Heilmittel-Richtlinie - Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung (HeilM-RL) [online]. 2021 [Accessed: 15.02.2021]. URL: https://www.g-ba.de/downloads/62-492-2324/HeilM-RL_2020-10-15_iK-2021-01-01.pdf.

21. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

Appendix A – Research question 1: results of the outcome "hospitalizations"

Table 6: Results of the outcome "hospitalizations", study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)

Study Outcome category Outcome	Nusinersen N	Nusinersen Adjusted annual rate [95% CI][a] Number of events	Sham intervention N	Sham intervention Adjusted annual rate [95% CI][a] Number of events	Nusinersen vs. sham intervention Rate ratio [95% CI][a]; p-value
ENDEAR					
Morbidity					
Hospitalizations[b]	*80*	*4.33 [3.61; 5.19]* *264*	*41*	*5.70 [4.39; 7.41]* *119*	*0.76 [0.55; 1.05];* *0.097*

a. Negative binomial regression with treatment and age at symptom onset and disease duration at screening as independent variables.
b. The frequency of hospitalizations for the following reasons was recorded: monitoring for general observation, symptoms after dosing/sham intervention under BSC, SAEs or additional investigations (e.g. planned surgery such as placement of a gastric feeding tube for preventive reasons).

BSC: best supportive care; CI: confidence interval; N: number of analysed patients; RCT: randomized controlled trial; SMA: spinal muscular atrophy; vs.: versus

Appendix B – Research question 2

B.1– Results of the outcome "hospitalizations" and of the AE outcomes "vomiting", "headache" and "back pain"

Table 7: Results (morbidity, side effects), study CHERISH – RCT, direct comparison: nusinersen vs. sham intervention, patients with later onset of disease (SMA type 2)

Study Outcome category Outcome	Nusinersen[a] N	Nusinersen[a] Adjusted annual rate [95% CI][b] Number of events	Sham intervention[a] N	Sham intervention[a] Adjusted annual rate [95% CI][b] Number of events	Nusinersen[a] vs. sham intervention[a] Rate ratio [95% CI][b]; p-value
CHERISH					
Morbidity					
Disease-related hospitalizations based on SAEs[c]	84	0.11 [0.06; 0.21] 11	42	0.28 [0.14; 0.54] 16	0.39 [0.15; 0.97]; 0.043
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Side effects					
Vomiting (PT, AE)	84	24 (29)	42	5 (12)	2.40 [0.99; 5.84]; 0.037[d]
Headache (PT, AE)	84	24 (29)	42	3 (7)	4.00 [1.28; 12.53]; 0.006[d]
Back pain (PT, AE)	84	21 (25)	42	0 (0)	21.75 [1.35; 350.55] < 0.001[d]

a. Treatment was to be against the background of concomitant supportive treatment. There is insufficient information on the implementation in the study to assume the best possible supportive therapy corresponding to the German health care context.
b. Negative binomial regression with treatment and age after screening as independent variables.
c. SAEs that required inpatient hospitalization or where hospitalization was prolonged; disease-related hospitalization was classified by a blinded committee.
d. Institute's calculation, unconditional exact test (CSZ method according to [21])

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMA: spinal muscular atrophy; vs.: versus

B.2 – Results of the long-term SHINE-CHERISH study

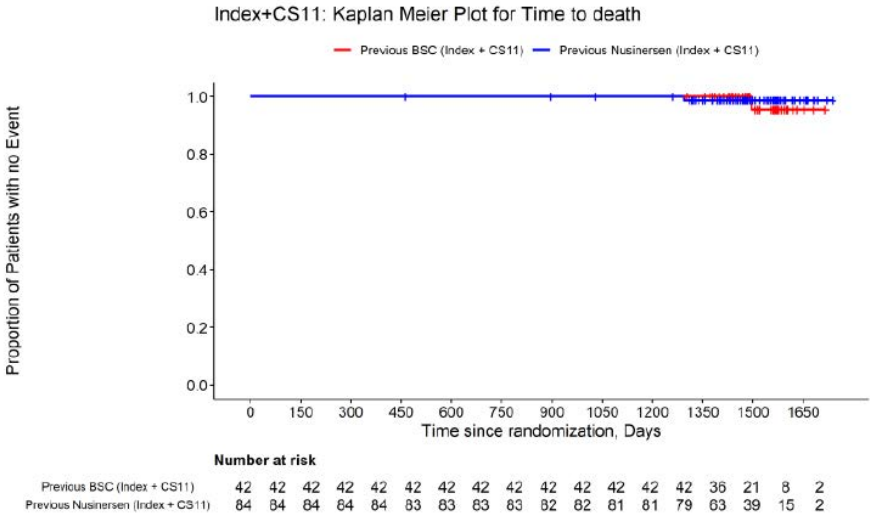

Figure 1: Kaplan-Meier curves for overall survival, SHINE-CHERISH study (study start with CHERISH), data cut-off: 27 August 2019

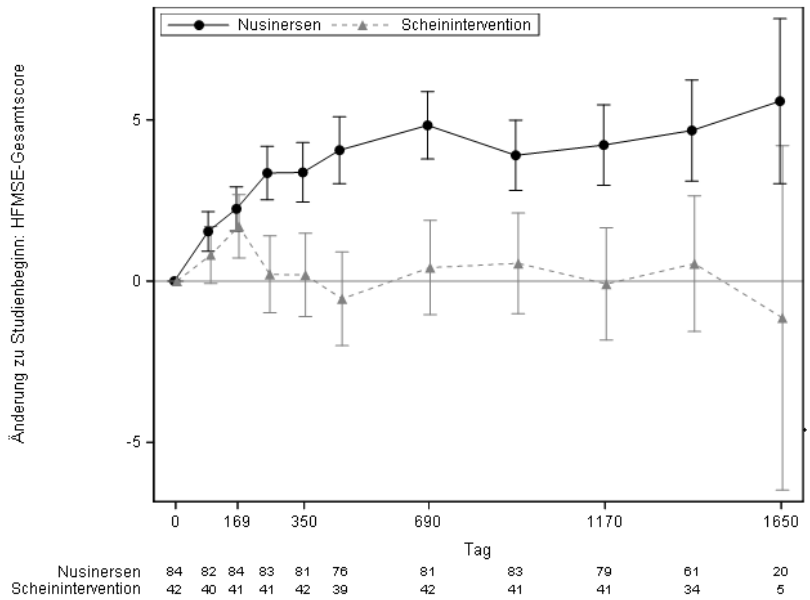

Figure 2: Curve for the outcome "HFMSE", SHINE-CHERISH study (study start with CHERISH), data cut-off: 27 August 2019

The figure shows the estimation of the mean change at baseline with standard deviation in the HFMSE total score in patients treated with nusinersen in both CHERISH and SHINE-CHERISH (black dots, nusinersen) and in patients who received a sham intervention in the CHERISH study and were treated with nusinersen in the SHINE-CHERISH study (grey triangles, sham intervention) as a function of time (days).

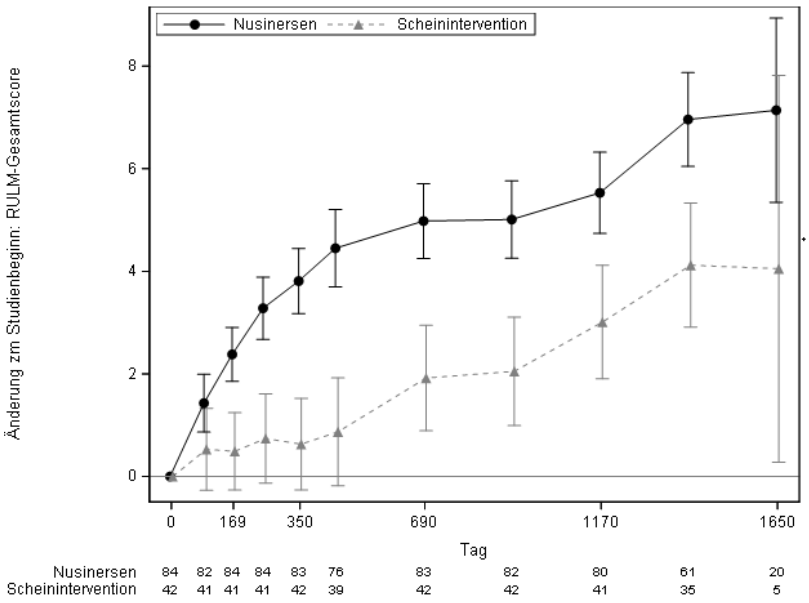

Figure 3: Curve for the outcome "RULM", SHINE-CHERISH study (study start with CHERISH), data cut-off: 27 August 2019

The figure shows the estimation of the mean change at baseline with standard deviation in the RULM total score in patients treated with nusinersen in both CHERISH and SHINE-CHERISH (black dots, nusinersen) and in patients who received a sham intervention in the CHERISH study and were treated with nusinersen in the SHINE-CHERISH study (grey triangles, sham intervention) as a function of time (days).

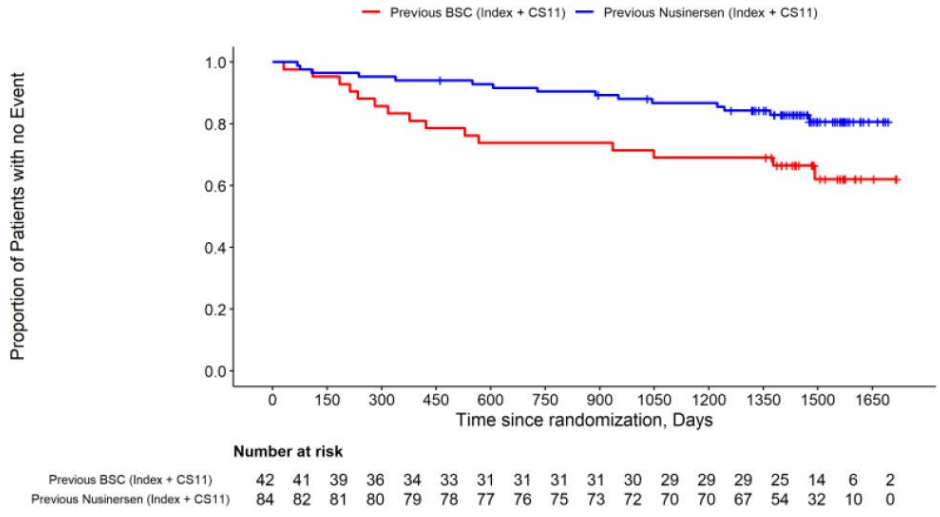

Figure 4: Kaplan-Meier curves for symptoms, serious respiratory events, SHINE-CHERISH study (study start with CHERISH), data cut-off: 27 August 2019