# Nusinersen MAA clinical eligibility criteria review

## Clarification questions

**Question 1**: The results given in file Biogen data on file - registries. 2020 are not adequate. They are an output from a statistics package with no background on methods used. They are therefore very hard to interpret. Could we please have either an interpretation of the results and/or have the methods used provided? Can you please specify which tests were used and a description of each variable?

## Real-world data from European registries

**Table 1: Overview of European registries**

| SMArtCARE | CuidAME | ISMAR |
|---|---|---|
| ▪ German-speaking countries<br>▪ Prospective non-randomised registry<br>▪ Standardised validated instruments<br>▪ Data collected during routine visits (4 months for nusinersen-treated, 6 months for untreated)<br>▪ E.g. assessed patient relevant endpoint: deaths, ventilation, HINE-2, CHOP INTEND, HFMSE, RULM, 6-MWT, scoliosis, AEs, AES due to therapy discontinuation, SAEs | ▪ Spain<br>▪ Under development<br>▪ 6 participating clinics<br>▪ Standardised validated instruments<br>▪ Retrospective and prospective monitoring of all SMA patients to evaluate drug influence and natural course of the disease | ▪ 3 separate registries: Italy, UK and USA<br>▪ 16 clinics<br>▪ Do not share one protocol<br>▪ Share harmonised data collection<br>▪ Evaluate influence of treatment |

Abbreviations: 6-MWT, 6-minute walk test; AE, adverse event; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Section 2; HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SAE, serious adverse event.

Real-world data on non-ambulant[1] type III patients were obtained from European SMA disease registries. Data from three registries were combined to conduct the analyses described in this submission. For an overview of all three registries see Table 1; more detailed information per registry is provided in the sections that follow. As the data presented in this section are the current data from these three European registries, it represents the real-world care that patients are currently receiving. No other treatment besides nusinersen is recommended at present (European consensus statement, 2020) (Kirschner, 2020).

[1] The definition for ambulation is 'able to walk without support for at least 10 metres.'

## Methodology

### *SMArtCARE (German-speaking countries)*

The main objective of the SMArtCARE registry (German Clinical Study ID: DRKS00012699) (SMArtCARE, 2020) was the evaluation of all people with 5q-SMA, regardless of their current treatment, as well as the planning and monitoring of therapeutic interventions in German-speaking countries (Germany, Austria, and Switzerland). It is therefore an indication-specific clinical registry.

The SMArtCARE registry was initiated prior to nusinersen approval but could not be launched until the necessary organisational and technical requirements were in place, which coincided with nusinersen launch. As in German-speaking countries, all patients who are eligible for treatment as per the summary of product characteristics receive nusinersen (European Medicines Agency, 2017), no data on patients receiving best-supportive care (BSC) only are available from the SMArtCARE registry (although all SMA patients − regardless of their care − are eligible for enrolment in this disease registry). However, data on untreated (BSC only) patients are available from the Italian ISMAR and Spanish CuidAME registry; thus data from these two registries were pooled with data from SMArtCARE for the analyses presented in this submission.

*Data acquisition*

The data collection was based on an international consensus for SMA registries (TREAT-NMD Neuromuscular Network, iSMAC) and took place as part of regular, clinically recommended routine visits of patients depending on their current treatment regimen. This also determined the time and frequency of the follow-up examinations. The standardised results were collected during routine visits at regular intervals of four (nusinersen treatment) or six months (max time frame recommended by guidelines). Case report forms (CRFs) were available for standardised follow-up. Electronic data were used for data capture with the aid of an electronic data capture (EDC) system. This system is a web-based data entry system administered by the Freiburg University Medical Center. SMArtCare Open App Platform was used and an OPEN app software called Clinical Insight. This software complies with the highest international standards for data protection and quality management (GDPR). OPEN App has developed several registries for rare and chronic diseases and is the official provider of European

reference networks (Clinical Patient Management System, ERN-CPMS). The data can be linked between different projects and registers.

*Data quality*

The quality of standardised data assessment in SMArtCARE is ensured through the use of standardised SMA-validated methods, by training staff in the use of the standardised questionnaires and by verifying data entry (see Table 2). SAS software is used to check the completeness, consistency and plausibility of the data. Data lock ensures that edits are tracked.

*Data collection training*

Site staff are trained prior to data entry and on a regular basis thereafter, up to four times a year. To ensure that data collection is consistent and comparable and to ensure valid monitoring based on consistent assessment across sites, two-day central training workshops for physiotherapists are also provided (Pechmann et al., 2019). Names of trained staff are stored in the OPEN App system. This shows in a transparent manner whether entries have been made by trained staff.

***ISMAR (Italy)***

The development of the registry of the International Consortium for Spinal Muscular Atrophy (iSMAC), a prospective cohort study entitled ISMAR (Register number: MER-SMA-18-00 ISMAC (FPG ID 1894, no website available) (Eugenio Mercuri et al., 2019), was the result of an ongoing collaboration between three large national networks in the US, Italy and UK in 16 locations (E. Mercuri et al., 2019; Nemours, 2020; SMA Reach UK, 2020). ISMAR prospectively collected harmonised data from patients with genetically confirmed 5q-SMA. The main purpose was to gain increased understanding of the disease and response to treatments. The data for the registry were collected as part of regular, clinically recommended, routine visits – depending on their current treatment regimen.

*Data acquisition*

The three countries operated according to a common electronic CRF (eCRF) with a common data dictionary. Only data from the Italian part of the register were used in the analyses presented in this submission. The US registry surveys were excluded because the transferability to the English healthcare context could not be ensured. The data from the UK part of the registry could not be included due to the limited availability of appropriate data (i.e., data on the paediatric type III SMA population, who lost ambulation in the 12 months prior to initiation of nusinersen treatment [as per MAA criteria] with sufficient follow-up; additionally, there were delays in centre setup/service delivery).

*Data quality*

Quality control of the ISMAR data was conducted and verified by a medical monitor, a clinical research assistant and a data manager.

*Data collection training*

Interoperator variability assessment takes place annually. Physiotherapists are trained at least once a year, and monthly teleconferences are held with the physiotherapists from the three networks (UK, US and Italy).

***CuidAME (Spain)***

This registry collected data from six clinics relevant to the care of people diagnosed with 5q-SMA (CuidAME, 2020). The SMArtCARE registry served as a model for its structure and organisation, with data collection aligned to the TREAT-NMD core minimum dataset. The alignment with SMArtCARE ensured that comparable criteria were used across institutions. All people with SMA, regardless of their current treatment, were monitored within CuidAME; it is therefore also an indication registry. This registry contained standardised and validated evaluations for documenting motor function in people with SMA. Data for the registry was collected as part of regular, clinically recommended, routine visits, depending on their current treatment regimen. The main purpose of the registry is to provide retrospective and prospective monitoring of all people with SMA to gain a better understanding of the natural course of SMA and the influence of drug treatment.

*Data acquisition*

CuidAME uses the same OPEN App software as the SMArtCARE registry, increasing data harmonisation across the registries.

This software meets the highest international standards of data protection and quality management (General Data Protection Regulation, GDPR). OPEN App has developed a number of registries for rare and chronic diseases and is an official provider of European reference networks (Clinical Patient Management System, ERN-CPMS). Data from different projects and registries can be combined. Data entry takes place every 6 to 12 months because untreated and treated patients show up for consultations at different intervals.

*Data quality*

The coordinating data manager has access to data from all sites to administer and monitor the data. Implementation of and compliance with quality assurance and control systems is based on Standard Operating Procedures (SOPs) and in line with Good Clinical Practice (GCP). The OPEN App system is used to check the data for completeness, consistency and plausibility. On-site inspection of the data by the data manager takes place annually.

*Data collection training*

The coordinating physicians and physiotherapists provide on-site training in standardised assessment of motor function using validated scores at new sites prior to initiation of data collection. Additional support is provided as needed as relevant questions emerge.

**Detailed description of quality criteria of the SMA disease registries**

The data quality criteria and data quality compliance criteria are presented in detail in Table 2. The registry operators were interviewed in writing in this regard. The extent to which the various criteria are met are indicated by ✓ (fully complies), (✓) (partly complies) and ☒ (does not comply).

**Table 2: Criteria for data quality and compliance with data quality criteria from the three SMA registries**

| Category | Quality criteria | SMArtCARE | ISMAR | CuidAME |
|---|---|---|---|---|
| Mandatory criteria for compliance with data quality | Detailed registry description (objective, registry protocol) | ✓ (Pechmann et al., 2019; SMArtCARE, 2017) | **(✓)** (ISMAR, 2019; E. Mercuri et al., 2019) | ✓ (CuidAME, 2019) |
| | Exact definition / operationalisation of exposures, clinical events, outcomes and confounders | ✓ | **(✓)** | ☒ |
| | Current data plan / coding manual | ✓[1] | ✓[1] | ✓ |
| | Training on data collection and documentation | ✓ | ✓[9] | ✓ |
| | Clearly defined inclusion and exclusion criteria for registry patients | ✓[2] | ✓[10] | ✓[2] (a and b excluded) |
| | SOP system for data collection | ✓[3] | ✓ | ✓ |
| | Measures to ensure data accuracy and information about error rates (e.g. source data verification, internal and external audits, IT-supported checks [e.g. cross reference checks]) | ✓[4] | ✓[11] | ✓ |
| | Documentation trail – documentation of changes in processes and definitions in the registry | ✓[5] | ✓[12] | ✓ |
| | Scientific independence of the registry | ✓[6] | ✓[13] | ✓ |
| | Sustainable funding | ✓ | ✓ | ✓ |
| Generally applicable criteria for registry studies for medicinal product benefit assessment purposes | Precise dates for patients, disease and events | ✓[7] | ✓[14] | ✓ |
| | Detailed information on the drug treatment (active substance, dose, dose modification, including dates) | ✓ | ✓ | ✓ |
| | Timeliness (up-to-dateness / rapid availability / punctuality of necessary results) | ✓ | ✓ | ✓ |
| General criteria that might be | Use of standard classifications (e.g. ICD-10) and terminologies (e.g. MedDRA) | ✓ | ✓[15] | ✓ |

| Category | Quality criteria | SMArtCARE | ISMAR | CuidAME |
|---|---|---|---|---|
| relevant for registry studies for benefit assessment purposes depending on the research question | Use of valid standard scoring systems (questionnaires, scales, tests) | ✓ | ✓ | ✓ |
| | Flexibility and adaptability (e.g. to embed studies, for additional data collection, if the healthcare setting changes) | ✓ | ✓ | ✓ |
| | Linkability to other data sources | ✓ | ☒[16] | ✓ |
| Criteria where degree of compliance depends on the research question | Representativeness of the sample / sample selection | ✓[8] | ✓[8] | ✓[8] |
| | Completeness of data per assessment timepoint (loss to follow-up, drop-outs) | ✓ | ✓ | ✓ |
| | Completeness of assessment timepoints | ✓ | ✓ | ✓ |
| | Data accuracy | ✓ | ✓ | ✓ |
| | Collection of all relevant confounders per research question | ✓ | ✓ | ✓ |
| | Data consistency over time | ✓ | ✓ | ✓ |

✓ (fully complies), (✓) (partly complies) and ☒ (does not comply)

[1]data dictionary available

[2] Genetically confirmed 5q SMA. Exclusion criteria are (a) Other types of SMA (not 5q SMA), (b) Patient does not have legal capacity to understand the content, meaning and implications of the registry, (c) Participating in a drug study, unless the sponsor explicitly permits the patient's inclusion.

[3] SOPs of the Clinical Trial Unit (CTU), Freiburg University Hospital

[4] CRFs have defined ranges of values. Regular data queries are performed and monitoring of selected sites/risk-based monitoring is planned.

[5] The registry has an audit trail that automatically traces any changes in the database, including author's name, time and date of change. Datasets can be "saved" and "completely saved". Once a dataset has been "completely saved", it is finalized. In the event of changes to a completely saved dataset, the reason for the change must be entered into the system before a dataset can be updated.

[6] The registry has an independent steering committee with clearly defined responsibilities (protocol). It consists of physicians of various patient groups (children/adults, countries) and patient advocates. No steering committee members have any financial interest.

[7] Precise dates are requested.

[8] All patients included in the registry were included in the analysis.

[9] The registry verifies that the location is trained in eCRF implementation at each visit. Staff also take part in annual training on reliable data entry and training on each new CRF version. Weekly checks for inconsistency and repeat training also take place. Training is documented in specific SOP protocols signed by clinical staff. The training log is saved at each site.

[10] 5q SMA patients. Patients who were or are in clinical trials are excluded from prospective data acquisition in the registry, with only demographic data or retrospective data (prior to inclusion) being taken into account.

[11] Data entry process status and review take place monthly. The supervisor of the coordinating locations checks data entry at least every 1 – 2 weeks to check query status, gather information about the process, discuss the most common data entry errors and announce when reports will be issued so that all the data is entered conclusively in the eCRF and checked beforehand . Additional activities include: Oversight over eCRF changes, participation in national and international CRF review meetings, preparing data reports and providing site support. A national supervisor additionally monitors data entry via Excel report on a weekly basis. The Excel report groups key information entered by each site, the aim being to identify missing values, data entry errors and inconsistencies. After data review, an email with the query is sent to the date entry staff of the site in question and findings are resolved. The week after review, the coordinator checks that the query was successfully resolved and implemented in the eCRF. Source documents are gathered and reported as per GCP. A delegation log specifying roles and responsibilities is kept at each site. If source documents are modified, correction is compliant with GCP rules.

[12] The ISMAC registries work with a web software system (CRF). In Italy all physicians, therapists, coordinators, managers, nurses and data entry staff complete and review the CRFs with the aid of the ISMAC registry. Every CRF update is assigned to a new version of the software. All versions, past and current, are stored in a software

| Category | Quality criteria | SMArtCARE | ISMAR | CuidAME |
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| repository and documented. The IT team and coordinators manage the documentation of the Italian data dictionary in which CRF changes are traced and have oversight over differences between the Italian CRF and a universal CRF for the consortium (golden source).<br>[13] Biogen provides resources for the registry and works with the registry but does not have intellectual property rights on the data and has no control over publication decisions.<br>[14] Anonymized data is used in analyses but precise data is available.<br>[15] as per ICD-9<br>[16] Because of the fact that the data pools are not linkable, the data is harmonised and the pooled data are assessed.<br><br>CTU = Clinical Trials Unit, eCRF = electronic Case Report Form, ICD = International Classification of Diseases and Related Health Problems, GCP = Good Clinical Practice, MedDRA = Medical Dictionary for Regulatory Activities, , SMA = Spinal Muscular Atrophy, SOP = Standard Operating Procedure | | | | |

Data consistency over time was ensured by conducting regular standardised data checks as described above. The formats and definitions of the data entered in the registry are consistent over time and across registries.

**Patient-relevant outcomes in the SMA registry**

Consistent and standardised assessment of motor function across facilities and between patients in the three registries presented is ensured by the use of validated motor function tests (e.g., HFMSE) to evaluate functional status in a standardised manner. The physiotherapists and physicians in all three registries were trained regularly to measure changes in disease course using the same set of standards. This expertise was achieved within the three registries by practical experience in clinical trials, provision of training, and participation in motor function test courses, ensuring comparability of the data from the three registries.

*Mortality*

Mortality data were not available for the current analyses. However, mortality is not deemed relevant as life expectancy is not usually affected in type III patients (Zerres et al., 1997).

*Morbidity*

Morbidity was assessed using validated motor parameters:

A. Hammersmith Functional Motor Scale – Expanded (HFMSE)

B. Revised Upper Limb Module (RULM)

These measurements were observed for a mean period of 18 months in the registries.

## Treatments

### *Nusinersen*

Treated patients received the recommended dosage of 12 mg (5 ml) per administration; four loading doses on Days 0, 14, 28 and 63, with a maintenance dose administered once every four months thereafter (European Medicines Agency, 2017).

### *Untreated (BSC only)*

Patients received the best available personalised treatment for relief of symptoms and improvement of quality of life (equivalent to BSC) (Finkel et al., 2018; Kleinschnitz, 2020; Mercuri, Finkel, et al., 2018).

## Registry study design and populations

Details of the registry design and population are shown in Table 3.

**Table 3: Characteristics of the registries**

| **Study** | **Study design <RCT, double-blind/single-blind/open-label, parallel/cross-over, etc.>** | **Population <relevant characteristics, e.g., severity>** | **Interventions (number of patients)** | **Study duration/ data cutoffs <if applicable: run-in, treatment, follow-up>** | **Where conducted** | **Primary outcome measure; patient-relevant secondary outcome measures** |
|---|---|---|---|---|---|---|
| SMArtCARE | An observational, prospective long-term registry of 5q SMA patients | Patients of any age | All approved drug and non-drug treatments.<br><br>Total type III non-ambulant patients: [redacted]<br><br>Nusinersen: [redacted]<br><br>BSC treatment: [redacted] | not applicable[1] | Germany, Austria, Switzerland (German-speaking area) | Evaluation of all patients regardless of current treatment and planning and monitoring of therapeutic interventions.<br>Definitions of a primary or patient-relevant secondary outcome measures are not provided in the registry, but the following patient-relevant outcomes are documented:<br>• Deaths<br>• Time to death<br>• Permanent ventilation<br>• HFMSE<br>• WHO motor milestones<br>• RULM<br>• 6MWT<br>• Wheelchair requirement<br>• Safety<br>• Hospitalizations |

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| | | | | | | • Surgical interventions<br>• Incidence of scoliosis<br>• Serious respiratory events<br>• AEs<br>• Treatment discontinuation due to AEs<br>• SAEs |
| ISMAR | An observational, prospective long-term registry of 5q SMA patients | Patients of any age | All approved drug and non-drug treatments.<br><br>Total type III non-ambulant patients: [redacted]<br><br>Nusinersen: [redacted]<br><br>BSC treatment: [redacted] | not applicable[1] | Italy | Evaluation of all patients regardless of current treatment and planning and monitoring of therapeutic interventions. Definitions of a primary or patient-relevant secondary outcome measures are not provided in the registry, but the following patient-relevant outcomes are documented:<br>• Deaths<br>• Time to death<br>• Permanent ventilation<br>• HFMSE<br>• WHO motor milestones<br>• RULM<br>• 6MWT<br>• Wheelchair requirement<br>• Safety<br>• Hospitalizations |

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| | | | | | | • Surgical interventions<br>• Incidence of scoliosis<br>• Serious respiratory events<br>• AEs<br>• Treatment discontinuation due to AEs<br>• SAEs |
| CuidAME | An observational, prospective long-term registry of 5q SMA patients | Patients of any age | All approved drug and non-drug treatments.<br><br>Total type III non-ambulant patients: [redacted]<br><br>Nusinersen: [redacted]<br><br>BSC treatment: [redacted] | not applicable[1] | Spain | Evaluation of all patients regardless of current treatment and planning and monitoring of therapeutic interventions. Definitions of a primary or patient-relevant secondary outcome measures are not provided in the registry, but the following patient-relevant outcomes are documented:<br>• Deaths<br>• Time to death<br>• Permanent ventilation<br>• HFMSE<br>• WHO motor milestones<br>• RULM<br>• 6MWT<br>• Wheelchair requirement<br>• Safety<br>• Hospitalizations |

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|---|---|---|---|---|---|---|
| | | | | | | • Surgical interventions<br>• Incidence of scoliosis<br>• Serious respiratory events<br>• AEs<br>• Treatment discontinuation due to AEs<br>• SAEs |
| [1] Data extraction study; data for all available patients was extracted | | | | | | |

### *Methods for assessment of the reliability of the evidence and synthesis of results*

The registries are classed as having a high overall risk of bias because the registry entries are neither randomised nor controlled. Nevertheless, selected aspects such as compliance with the intention-to-treat (ITT) principle were assessed at outcome level. At outcome level, data analysis issues, reporting issues and other potential sources of bias were also taken into account.

The methodologies of the included registries were rated based on Transparent Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) criteria. The rating criteria were presented in full according to the specifications in Table 4.

**Table 4: Assessment of the methodology of the registries using the RECORD criteria**

| Item | Characteristic | SMArtCARE | ISMAR | CuidAME |
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| 2 | Rationale | Longitudinal Data Collection from Patients with SMA: The SMArtCARE Database<br>Establishment of a prospective registry (SMArtCARE) to collect routine clinical data in order to examine the natural course of the disease in patients with SMA and to systematically present treatment effects | ISMAR prospectively collects harmonized data from patients with genetically confirmed 5q-SMA. The main purpose is to learn more about the disease and response to treatments. | Longitudinal data collection from patients with spinal muscular atrophy in a national registry in Spain |
| 3 | Objective | The main goal of the independent SMArtCARE registry is to evaluate all 5q-SMA patients, regardless of their current treatment, as well as to plan and monitor therapeutic interventions.<br>The register is not based on any specific hypotheses. | This large collaborative registry creates a structured but flexible system for collecting prospective data that maps all patients with SMA and monitors them over the course of several years. | Establishment of a registry (CuidAME) to record routine clinical data in order to examine the natural course of the disease in patients with SMA and to systematically present treatment effects. |
| 4 | Design | SMArtCARE is a prospective, multicentre, non-randomised registry in German-speaking countries.<br>The data for the registry is collected during each routine clinical visit to the SMA patient. Data obtained during regular patient visits prior to inclusion in the registry were documented retrospectively. | ISMAR is a prospective, multicenter, non-randomised registry in Italy, the UK and the USA | CuidAME is a retrospective and prospective, multicenter, non-randomized registry in Spain |
| 5 | Setting and location of the study; Relevant timing information, including periods of recruitment, | The data collection is based on an international consensus for SMA registries (TREAT-NMD, iSMAC). Data for the registry is collected as part of regular, clinically recommended, routine visits to patients depending on their current treatment regimen. The timing and frequency of follow-up examinations | Data is collected from 16 locations in Italy, the UK and the USA.<br>The first patient was included in 2017. The registry collects data on all patients diagnosed with 5q-associated SMA.<br>The ISMAC registry is a web software system that hosts the ISMAC Case Report Form (CRF) and is referred to as | Data are collected from six centers in Spain.<br>The first patient was included in the registry in February 2019. The first annual report was published in December 2019. The legality of data collection and use is based on a declaration of consent signed by each |

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| | exposure, follow-up and data collection | depend on the current treatment regimen.<br>Electronic data are used for data capture with the aid of an electronic data capture (EDC) system. This system is a web-based data entry system administered by the Freiburg University Medical Center.<br>Data is collected from 50 centers in Germany, Austria and Switzerland.<br>The first patients were added to the registry in the first quarter of 2018. The follow-up phase should last as long as possible.<br>The registry collects data on all patients with 5q-associated SMA. The patients are divided into defined cohorts according to their disease characteristics. | the Registro ISMAC-NMD registration portal and is based on copyrighted software developed by Astir. In Italy, all registry staff fill and review CRFs using the ISMAC registry.<br>Due to the nature of the data collection, the observation periods differ between patients. Corresponding statistical models have taken this into account (Biogen, 2020). | patient. The data are pseudo-anonymized: each patient is identified in the register by a unique patient identification code (patient number). |
| 6 | Participants | Inclusion criteria:<br>• Genetically confirmed diagnosis of 5q-associated SMA<br>• Written consent from the patient or legal guardian<br>Exclusion criteria:<br>• Other SMA types (not 5q-associated SMA)<br>• Patients with no legal capacity who are unable to understand the nature, scope and potential consequences of participating in the registry | Inclusion criteria:<br>• Genetically confirmed diagnosis of 5q-associated SMA<br>• Written consent from the patient or legal guardian<br>Exclusion criteria:<br>• Other SMA types (not 5q-associated SMA)<br>• Patients with no legal capacity who are unable to understand the nature, scope and possible consequences of the registration | Inclusion criteria:<br>• Genetically confirmed diagnosis of 5q-associated SMA<br>• Written consent from the patient or legal guardian<br>Exclusion criteria:<br>• Other SMA types (not 5q-associated SMA)<br>• Patients with no legal capacity who are unable to understand the nature, scope and possible consequences of the registration |
| 7 | Variables | All data available in the registry are extracted for all 5q-SMA patients. | Data for 5q-SMA | Data for 5q-SMA |
| 7a | List of the codes and algorithms | Patient identification:<br>The department for clinical studies in Freiburg is informed about newly | N/A | The data are pseudo-anonymized. A unique patient identification code (patient number) is assigned to each |

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| | used to classify exposures, outcomes, confounders and effect modifiers | admitted patients with a registration form. Each patient is identified in the register by a unique patient identifier (patient number). A system to avoid duplicate patient entries is implemented. Each center keeps a patient identification record with the names of all patients in the registry and the corresponding identification codes.<br>Co-medication:<br>The co-medication is encoded using the Anatomical Therapeutic Chemical (ATC) code in its latest version. The coding is based on the given active ingredient or trade name. | | patient. A system to prevent duplicate patient entries is implemented. Data security is guaranteed in accordance with national and European law (General Data Protection Regulation (EU) 2016/679 ("GDPR")). |
| 8 | Data sources | Basic patient information (annually):<br>• Medical history and basic information<br>Results of genetic tests (type of SMN1 mutation (e.g. deletion / point mutation), SMN2 copy number, mutations in other known genetic modifiers, if applicable)<br>• Age at onset of symptoms<br>• Age at diagnosis<br>• Need for mechanical ventilation or nutritional support<br>• Medication<br>• Concomitant medication<br>• Complementary therapies (e.g. physiotherapy)<br>• Medical history (including operations)<br>• Family history<br>Follow-up information for routine patient visits:<br>Current medical history | • The following questions are asked in the form of interviews:<br>o medical history<br>o History of operations<br>o Use of medication<br>o Demographic information (date of birth, gender, place of residence)<br>o Genetic information (information on SMA, result of the genetic tests 5q-associated SMA)<br>o Therapies received<br>o Medication taken<br>o Administration of Nusinersen (Spinraza®) and occurrence of side effects on the spine or which can be attributed to the drug itself<br>• Physical examination:<br>o weight<br>o size<br>o blood pressure | The following is recorded within the register:<br>• Ventilation status<br>• Nutritional status<br>• Orthopaedic symptoms (including pain, fatigue, and adverse events)<br>• Clinical examination (including motor milestones and growth parameters in paediatric patients)<br>• CHOP INTEND<br>• HFMSE<br>• RULM<br>• 6MWT |

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| | | • Lung symptoms and function (use of mechanical ventilation (hours per day), tracheotomy, peak cough flow, vital capacity, use of cough aids)<br>Nutrition<br>• Using a feeding tube<br>• Percentage of oral food intake<br>Orthopaedic symptoms<br>• pain (with localization)<br>• Scoliosis: Cobb angle, surgery<br>Fatigue<br>Adverse Events of Special Interest<br>• death (cause of death)<br>• Hospitalization (reason, duration and need for mechanical ventilation)<br>• Life threatening<br>• Correlation with drug treatment<br>Changes to concomitant drugs and therapies<br>History of motor milestones according to WHO<br>Self-assessment by patients or their parents regarding the course of the disease<br>Patient-reported endpoints (patient reported outcomes, PROs, quality of life / burden on caregivers)<br>Clinical examinations<br>growth<br>• First patient visit: body weight and height<br>• Tracking of body weight with each visit<br>• For pediatric patients, keep track of height and head circumference at each visit until they are fully grown | o Heart rate and breathing rate<br>o general physical examination<br>o detailed neurological examinations<br>o Standard motor examination (movement assessment by physiotherapists)<br>o Motor skills questionnaires<br>• Physiotherapy tests:<br>o Assessment of strength<br>o Evaluation of joint flexibility<br>o Assessment of muscle function<br>o SMA-specific motor function scales (e.g. HFMSE) | |

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| | | Vital signs<br>• Oxygen saturation<br>• heart rate<br>• blood pressure<br>Physical examination<br>• Skin<br>• throat, nose and ears<br>• lungs<br>• Heart<br>• Belly<br>• genitals<br>• Neurology<br>Assessment of motor skills<br>WHO engine milestones and / or HINE subscale 2<br>• Head posture<br>• Sit<br>• crawling<br>• Stand<br>• Go<br>Physiotherapeutic reviews:<br>• SMA type 1: CHOP INTEND<br>• HFSME (if CHOP INTEND> 50 points)<br>• SMA type 2-4: HFSME, RULM, 6 MWT (for ambulatory patients)<br>• Optional for adult patients: ALS functional rating scale<br>Drug treatment (if applicable)<br>• Performing a lumbar puncture<br>• Need for additional sedation or general anaesthesia<br>• Vital functions after lumbar puncture<br>• Adverse events resulting from the procedure | | |

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| | | • Information on post-puncture headache<br>Adverse events / drug side effects<br>Adverse events of particular interest are collected during each visit and documented in the CRF in a specific UE section. In patients with regular follow-up care, adverse events of particular concern include all serious adverse events that resulted in death, life threatening, or hospitalization. For patients receiving treatment, adverse events of particular concern additionally include possible treatment-related medical events. | | |
| 9 | Bias | A selection bias appears unlikely, since all patients for whom data were available in the registry centres up to the data cut-off were included in the analysis.<br>In order to avoid a selection bias, the doctors were asked to consistently include the patients according to inclusion and exclusion criteria. The department for clinical studies in Freiburg is informed about newly admitted patients with a registration form. Each patient is identified in the register by a unique patient identifier (patient number). A system to avoid duplicate patient entries was implemented. Each centre keeps a patient identification record with the names of all patients in the registry and the corresponding identification codes.<br>Conservative methods such as multiple imputation or Markov Chain Monte Carlo were used to impute missing values. | A selection bias appears unlikely, since all patients for whom data were available in the registry centres up to the data cut-off were included in the analysis.<br>Due to the design of the registry, the results are potentially skewed. They represent the best currently available evidence with longitudinal data on the course of the disease and treatment influence of Nusinersen in type III non-ambulant patients. The instruments used to measure disease progression have been validated. | A selection bias appears unlikely, since all patients for whom data were available in the registry centres up to the data cut-off were included in the analysis. |

| | | | | |
|---|---|---|---|---|
| | | Due to the register design, the results are potentially biased. They represent the best currently available evidence with longitudinal data on the course of the disease and treatment influence of Nusinersen in type III non-ambulant patients. The instruments used to measure disease progression have been validated. | | |
| 10 | Study size | The study size is determined by the number of patients available in the centres, taking into account the rarity of the disease. There is therefore no sample size estimation.<br>The aim of the registry is to record the data on SMA patients as completely as possible by including all SMA patients in German-speaking countries. It is expected that a total of around 1000 patients will be enrolled in the registry. | No sample size calculation is performed as this registry aims to capture the data of SMA patients as completely as possible by including all SMA patients from the Italian registry. it is expected that a total of approximately 800 patients will be enrolled in the registry. | The study size is determined by the number of patients available in the centres, taking into account the rarity of the disease. There is therefore no sample size estimation.<br>Approximately 450 patients will be included in the registry, regardless of age or gender. |
| 11 | Quantitative variables | Investigations<br>growth<br>• First patient visit: body weight and height<br>• Tracking of body weight with each visit<br>• For paediatric patients: Track height and head circumference at each visit until they are fully grown<br>Physiotherapeutic reviews:<br>• SMA type 1: CHOP INTEND<br>• HFSME (if CHOP INTEND> 50 points)<br>• SMA type 2-4: HFSME, RULM, 6MWT (for ambulatory patients)<br>• Optional for adult patients: ALS functional rating scale | The main objective of this registry is to document all patients diagnosed with 5q-SMA. The statistical analysis will be mainly descriptive. | • Clinical examination (including motor milestones and growth parameters in paediatric patients)<br>• CHOP INTEND<br>• HFMSE<br>• RULM<br>• 6MWT |

| | | | | |
|---|---|---|---|---|
| | | An increase in the respective instruments indicates a better condition. | | |
| 12 | Statistics | The main objective of this registry is to document all patients diagnosed with 5q-SMA. The statistical analysis will be mainly descriptive.<br>a) Continuous variables are calculated according to the arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum and the number of complete and missing observations Variables can also be represented in categories. Relative frequencies are indicated by the total number in%. Medical data documented at different times, e.g. Laboratory data are summarized. Univariate and multivariate regression analyses are performed to assess the effect of age at the start of treatment, SMN2 copy number, and motor function, which are either CHOP INTEND, RULM, HFMSE score, 6MWT, WHO motor milestones or ALS- FRS-R are defined. Multivariate regression analysis with backward selection of the variables (p = 0.1) was performed. A Spearman correlation analysis is used for correlation analysis.<br>b) Patients are divided into cohorts according to disease characteristics, and analyses are performed in these subgroups if> 10 patients are observed in a cohort.<br>c) Unless otherwise specified in individual cases, missing values are not replaced and only observed cases are analysed. Partially missing data is | The main objective of this registry is to document all patients diagnosed with 5q-SMA. The statistical analysis will be mainly descriptive. | The statistical analysis will be mainly descriptive. First, the data quality is assessed based on the number of recruits and the completeness of the data (percentage of missing values). The time to the event is estimated using the Kaplan-Meier method. Continuous data are grouped according to the arithmetic mean, standard deviation, minimum, 25% quartile, maximum, and the number of complete and missing observations. If necessary, continuous variables can also be represented in categories. Categorical data are grouped according to the total number of patients in each category and the number of missing values. Relative frequencies are shown as a percentage.<br>Analyses on specific research questions can be carried out on request and are described in a specific statistical analysis plan. |

| | | | | |
|---|---|---|---|---|
| | | handled as follows: If the day of a date variable is unknown, the value "15" is inserted as the day and a footnote is displayed in the listings that the day was unknown. If the day and month of a date variable are unknown, July 1 is inserted as the day and month, and a footnote appears in the listings indicating that the day and month were unknown. If a date is completely missing, it will not be inserted. | | |
| 12a | Data access and cleaning methods | The lead investigator and the CTU are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.<br>An independent Data Monitoring Committee (DMC) and a steering committee have been established.<br>The role of the DMC / steering body is to monitor the progress of the register. In addition, the DMC / steering committee decides on specific analyses within the register. If necessary, the DMC / steering committee gives the coordinating investigator a recommendation to change or update the registry. The underlying principles for the DMC are ethical and scientific aspects for research within the SMA indication.<br>For this purpose, the DMC must be informed about compliance with the protocol and the corresponding documentation, as well as about patient recruitment. The DMC receives the regular analysis report at the planned analysis times. | Quality control in Italy is carried out by a clinical research assistant and a data manager. Physiotherapists are trained once a year and monthly conference calls are held with physiotherapists from the three networks (UK, USA and Italy). Interoperator variability tests take place annually. | A system will be implemented to prevent duplicate patient entries. Each centre keeps a patient identification protocol with the names of all patients in the registry, with each patient being assigned the appropriate identification code. Data security is guaranteed in accordance with national and European law. |

| | | | | |
|---|---|---|---|---|
| 12b | Linkage | Information not available | Information not available | Information not available |
| 22 | Financials | Biogen provides financial support for the SMArtCARE registry. This source of funding did not play a role in the design of this register and will not play a role during the implementation, analysis, interpretation of the data or the decision to submit the results. Additional funding from other sources could be possible in the future to ensure the long-term sustainability of the registry. | Biogen provides funding to the registry and works with the registry but has no intellectual property on the data or controls decisions about publication. | Biogen provides financial support for the CuidAME registry. This source of funding did not play a role in the design of this register and will not play a role during the implementation, analysis, interpretation of the data or the decision to submit the results. Additional funding from other sources could be possible in the future to ensure the long-term sustainability of the registry. |

## *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

### *Overview of statistical analyses*

An overview of the statistical analyses across the European registry studies is presented in Table 5. The pre-specified statistical analysis plan for evaluation of data from the three registries defined the duration, type, extent, evaluation, format and methodology of patient-relevant outcomes and their capture (Biogen, 2020). For sensitivity analyses, a Piecewise linear mixed-effects model was used in addition to the prespecified Standard linear mixed model.

**Table 5. Summary of statistical analyses – registries**

| Study name | European registries[2] |
|---|---|
| Hypothesis objective | • H0: nusinersen treatment = no DMT<br>• H1: nusinersen treatment ≠ no DMT |
| Statistical analysis | • Mixed-effects model (nusinersen vs DMT-untreated)<br>• Piece-wise linear analysis (HFMSE and RULM scores) |
| Data management, patient withdrawals | • The completeness of the data for each survey time (loss-to-follow-up, drop-outs) and the completeness of the survey times are ensured by using the mixed effect model<br>• The implementation and maintenance of quality assurance and quality control systems is carried out through written SOPs and in accordance with GCP<br>• The data is checked for completeness, consistency and plausibility. |

The sample is fully representative because all type III non-ambulant SMA patients with complete data who were included in the three registries were incorporated in the data analysis. The completeness of data per assessment timepoint (loss to follow-up, drop-outs) and completeness of the assessment timepoints is ensured using a mixed effects model. The analysis set for the European registries is shown in Table 6.

**Table 6. European registries analysis set**

| Analysis population | Description |
|---|---|
| FAS | All participants with baseline (V0) data available |
| Abbreviations: FAS, full analysis set | |

### *Potential confounding factors*

Relevant confounders in SMA: age at symptom onset, sex, *SMN2* copy number, disease duration, registry, age at baseline and baseline scores using the respective scoring system were identified through the literature and consultation with two independent experts. These statistical and disease-specific confounders were adjusted for in the statistical models.

### *Analyses*

In the analysis (data cut-off: August 2020) HFMSE and RULM scores were assessed using a standard linear mixed model. The model was fit among both treated and untreated patients using outcome data collected after treatment initiation (for treated patients) or after the assigned index date (for untreated patients). The model estimated slopes of change over time separately in each treatment group, thus permitting assessment of whether the trajectory of the outcome over time differed between treated and untreated patients. Results were expressed as estimated change in pts/week (95% CI) and slopes were adjusted for important covariates.

Statistical analyses were performed using SAS, version 9.4 (SAS institute, Cary, NC).

#### *Standard linear mixed model*

A standard linear mixed model was developed to compare the trajectories of motor function scores between treated and untreated patients. In these models, time was defined as time since initiation of nusinersen (for the treated patients) or time since the assigned index data for untreated patients. Terms for treatment status (treated or untreated), time, and the interaction between treatment status and time were included in the model to allow for the estimation of separate slopes within each treatment group.

The dependency in the data due to repeated measures was accounted for by a random intercept per individual and an autoregressive covariance R matrix was used as correlation structure. The default estimation method REML was used for the covariance parameters. The Kenward Roger method was used to compute the degrees-of-freedom for the tests of fixed effects. The structure of the models was kept uniform with regards to the fixed- and random-effects structure.

Missing values at baseline (Hammersmith score, RULM score) were imputed using linear interpolation based on pre-treatment measures.

We adjusted the model using the following confounders:

- Age at onset (Onset ≥ 3 years vs Onset < 3 years)

- Sex (Male gender vs Female)

- -*SMN2* copy number

- Disease duration

- Registry (Italy=0; Germany=1; Spain=2)

- Age at baseline

- Baseline score value

As random effect we had intercept per individual.

*Piecewise linear mixed-effects model (Bovis, 2020)*

The standard mixed-effects model requires a parallel group of untreated patients for whom the trajectories of the outcomes can be compared against those of the treated group. As there were very few untreated patients, analyses using a piecewise linear mixed-effects model were additionally carried out for the treated group to assess whether the treatment impacted the trajectory of the outcome over time. For this analysis in nusinersen-treated patients, the slope prior to treatment initiation was compared with the slope after treatment initiation in the treated cohort of patients.

Conventional linear longitudinal models typically involve a single growth profile to represent linear changes in an outcome variable across time, which sometimes does not fit the empirical data. One solution is to introduce higher-order polynomials in time. However, the parameters are difficult to interpret.

As an alternative, linear spline models are a very useful and flexible way to accommodate many of the non-linear trends. The piecewise linear mixed-effects models allow different linear functions of time corresponding to the pre- and post-critical time point trends. By dividing the time axis into 2 or more segments and fitting a linear model in each of the segments, linear spline models sufficiently accommodate many of the non-linear trends. The break point, also called knot, is either decided by theory-driven hypothesis or data-driven graphical representations. In our analysis the treatment start date was considered as break point. Once the knot is set, a time spline

variable should be created based on time and knot to fit the piecewise linear mixed-effects model (Fitzmaurice et al., 2004).

$time\ spline = 0\ if\ t \leq k$

$t - k\ if\ t > k$

A piecewise linear mixed model was developed to consider the impact of the treatment on the functional ability scores. In the models to be presented the time of the treatment start was considered as the break point and we investigated if there was a significant difference between the slope before treatment start and the slope after treatment start (time spline).

The dependency in the data due to repeated measures was accounted for by a random intercept per individual and an autoregressive covariance R matrix was used as correlation structure. The default estimation method REML was used for the covariance parameters. The Kenward Roger method was used to compute the degrees-of-freedom for the tests of fixed effects. The structure of the models was kept uniform with regards to the fixed- and random-effects structure.

Missing values at baseline (HFMSE score, RULM score) were imputed using linear interpolation based on pre-treatment measures.

We adjusted the model using the following confounders:

- Age at onset (Onset ≥ 3 years vs Onset < 3 years)
- Sex (Male gender vs Female)
- *SMN2* copy number
- Disease duration
- Registry (Italy=0; Germany=1; Spain=2)
- Age at baseline
- Baseline score value

As random effect we had intercept per individual.

## *Clinical effectiveness results*

### Patient disposition

In total 375 patients with type III SMA from three different registries (Italian, German and Spanish) make up the overall registry study population (

**Figure *1***).

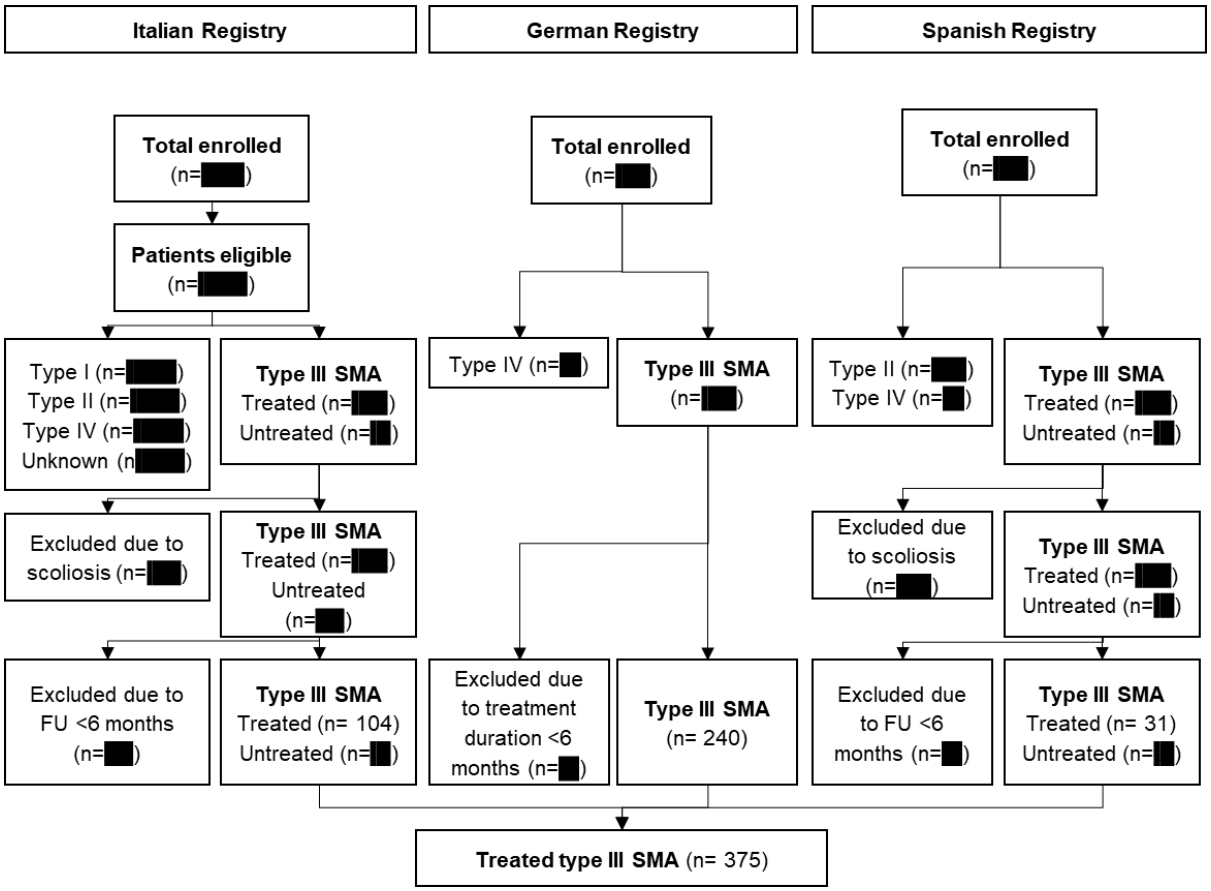
Within the Italian registry [redacted] patients were enrolled, of whom [redacted] were eligible and [redacted] were excluded. Of these [redacted] patients, [redacted] patients had type III SMA. Within this subgroup, [redacted] were treated with nusinersen and [redacted] were left untreated. Thirty-six of the untreated group were excluded due to scoliosis, leaving [redacted] patients. Of these [redacted] patients, [redacted] were treated and [redacted] were untreated with a further [redacted] being excluded due to being followed-up less than six months from starting treatment. This allowed 104 treated patients to be used for the overall study population.

Untreated patients with conditions such as scoliosis or scoliosis surgeries (spinal instrumentation, spinal fusion) that may preclude intrathecal treatment with nusinersen were excluded from analyses as they may not be directly comparable to treated patients.

Within the German registry, [redacted] patients were enrolled and treated with nusinersen, of whom [redacted] had type IV SMA and [redacted] had type III SMA. Of these [redacted] patients, [redacted] were excluded due to their treatment duration being less than six months. This allowed 240 treated patients to be used for the overall study population.

Within the Spanish registry, [redacted] patients were enrolled, of whom [redacted] had type II SMA, [redacted] had type IV SMA and [redacted] had type III SMA. Of these [redacted] patients, [redacted] were treated with nusinersen and [redacted] were untreated. [redacted]of the untreated patients were excluded due to having scoliosis, leaving [redacted] untreated patients. Out of the remaining [redacted] patients, [redacted] patient was excluded due to being followed-up less than six months from starting treatment, leaving [redacted] untreated patients and 31 treated patients. This allowed the 31 treated patients to be used for the overall study population.

**Figure 1. Registry data: Disposition of patients – flow diagram**




## Patients with non-ambulant type III SMA

The population of interest within the registries included people with non-ambulant type III SMA from Germany (n=[redacted]), Italy (n=[redacted]) and Spain (n=[redacted]). A comparison of nusinersen-treated (n=159) with untreated patients (BSC alone; n=9) will be presented in the overall non-ambulant type III cohort. Additional analyses presented were conducted on the sub-cohort, which included all enrolled individuals with non-ambulatory type III SMA, who were treated with nusinersen and had ≥1 visit prior to nusinersen initiation and ≥6 months follow-up (n=[redacted]). Both paediatric (n=[redacted]) and adults (n=[redacted]) with non-ambulant type III SMA were included in the sub-cohort analysis.

## Baseline characteristics

Based on the availability of data and requirements for the analysis, baseline data for the overall cohort and a sub-cohort are presented. The overall cohort included all enrolled individuals with non-ambulant type III SMA (n=168; nusinersen-treated n= 159); baseline characteristics are presented in

Table *7*. Within this cohort, 39% of treated patients had scoliosis at initiation, as opposed to 0 in the untreated arm.

**Table 7. Baseline characteristics, European registries – non-ambulant type III SMA (overall cohort)**

| **Baseline characteristics** | **All (n=168)** | **Treated (n=159)** | **Untreated (n=9)** |
|---|---|---|---|
| **Gender, M/F n (%)** | 94/74 (56/44) | 91/68 (57/43) | 3/6 (33/67) |
| **Registry, n (%)** | | | |
| *German* | [redacted] | [redacted] | [redacted] |
| *Italian* | [redacted] | [redacted] | [redacted] |
| *Spain* | [redacted] | [redacted] | [redacted] |
| ***SMN2* copies, n (%)** | | | |
| *1* | 0 (0) | 0 (0) | 0 (0) |
| *2* | 14 (8) | 14 (9) | 0 (0) |
| *3* | 67 (40) | 62 (39) | 5 (56) |
| *4* | 53 (32) | 52 (33) | 1 (11) |
| *> 4* | 1 (0.6) | 1 (0.6) | 0 (0) |
| *Unknown* | 33 (20) | 30 (19) | 3 (33) |
| **Adult patients at V0, n (%)** | [redacted] | [redacted] | [redacted] |
| **Age at symptom onset, n (%)** | | | |
| *< 3 years* | 106 (64) | 101 (64) | 5 (56) |
| *≥ 3 years* | 60 (36) | 56 (36) | 4 (44) |
| **Disease duration, years**, mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |
| **Age at first dose of treatment, years**, mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |
| **Age at last dose of treatment, years,** mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |
| **Age at last follow-up, years,** mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| **Number of doses,** mean ± SD; Median (min–max) | 7.16 ± 2.70<br>8.00 (1.00–12.00)<br>N=159 | 7.16 ± 2.70<br>8.00 (1.00–12.00) | NA |
| **Feeding** | | | |
| *Unsupported* | | | |
| *Oral, no supplements needed* | 11 (6) | 11 (7) | - |
| *Oral intake solids* | 13 (8) | 8 (5) | 5 (56) |
| *No feeding tube* | 47 (28) | 43 (27) | 4 (44) |
| **Baseline characteristics** | **All (n=168)** | **Treated (n=159)** | **Untreated (n=9)** |
| **Motor function** | | | |
| *HFMSE score, mean ± SD; Median (min–max)* | 17.93 ± 13.48<br>16.00 (0.00–59.00)<br>N=121 | 17.32 ± 13.15<br>15.00 (0.00–59.00)<br>N=117 | 35.75 ± 11.79<br>33.50 (24.00–52.00)<br>N=4 |
| *RULM score mean ± SD; Median (min–max)* | 22.83 ± 8.58<br>24.00 (0.00–37.00)<br>N=115 | 22.68 ± 8.67<br>24.00 (0.00–37.00)<br>N=111 | 27.25 ± 3.50<br>29.00 (22.00–29.00)<br>N=4 |
| **Number of subjects who use a wheelchair** | N=155 | N=151 | N=4 |
| *Yes (full-time/part-time), n(%)* | 81/11 (92.9/7.1) | 81/11 (89.8/7.2) | 4 (100) |
| *No* | 11 (7.1) | 11 (7.2) | 0 (0) |
| **Non-invasive ventilation** | 20 (11.90) | 18 (11.32) | 2 (22.22) |
| **Ventilator support** | N=14 | N=12 | N=2 |
| *Daily/weekly* | 4 (29) | 3 (25) | 1 (50) |
| *Night* | 6 (43) | 5 (42) | 1 (50) |
| *Yes (8h)* | 2 (14) | 2 (17) | - |
| *Other* | 2 (14) | 2 (17) | - |
| **Scoliosis** | | | |
| *Yes* | 62 (36.91) | 62 (38.99) | 0 (0.00) |
| *No* | 106 (63.09) | 97 (61.01) | 9 (100.00) |
| **Serious respiratory events**[1] | | | |
| *n (%)* | 1/144 (0.69) | 1/140 (0.71) | 0/4 (0.00) |
| *Events* | 1 | 1 | 0 |
| *Total subject months (in registry)* | 1728 | 1680 | 48 |

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; Max, maximum; Min, minimum; SD, standard deviation; SMA, spinal muscular atrophy; SMN, spinal motor neuron; RULM, Revised Upper Limb Module; V0, start treatment.
Notes: [1] in the 12 months before baseline (V0) based on medical records If data was not available in all patients the number of patients it was available in is listed (per item).

The sub-cohort included all enrolled individuals with non-ambulant type III SMA, who were treated with nusinersen and had ≥1 visit prior to nusinersen initiation and ≥6

months follow-up (n=[redacted]). Baseline characteristics of the sub-cohort are presented in Table 8.

**Table 8. Baseline characteristics – non-ambulant type III SMA (sub-cohort, n=[redacted]) [c]**

| Category | n (%) | Mean ± SD | Median (min–max) |
|---|---|---|---|
| **Gender, M/F** | [redacted] | [redacted] | [redacted] |
| **Registry** | | | |
| *German* | [redacted] | [redacted] | [redacted] |
| *Italian* | [redacted] | [redacted] | [redacted] |
| *Spain* | [redacted] | [redacted] | [redacted] |
| **Number of *SMN2* copies** | | | |
| *2 copies* | [redacted] | [redacted] | [redacted] |
| *3 copies* | [redacted] | [redacted] | [redacted] |
| *4 copies* | [redacted] | [redacted] | [redacted] |
| *Unknown* | [redacted] | [redacted] | [redacted] |
| **Category** | **n (%)** | **Mean ± SD** | **Median (min–max)** |
| **Adult patients at V0** | [redacted] | [redacted] | [redacted] |
| **Age at symptom onset** | [redacted] | [redacted] | [redacted] |
| *< 3 years* | [redacted] | [redacted] | [redacted] |
| *≥ 3 years* | [redacted] | [redacted] | [redacted] |
| **Disease duration, years (n=50)** | [redacted] | [redacted] | [redacted] |
| **Age at first dose of treatment, years** | [redacted] | [redacted] | [redacted] |
| **Age at last dose of treatment, years** | [redacted] | [redacted] | [redacted] |
| **Age at last follow-up, years** | [redacted] | [redacted] | [redacted] |
| **Number of doses** | [redacted] | [redacted] | [redacted] |
| **Feeding** | | | |
| *Unsupported* | [redacted] | [redacted] | [redacted] |
| *Oral, no supplements needed* | [redacted] | [redacted] | [redacted] |
| *Oral intake solids* | [redacted] | [redacted] | [redacted] |
| *Feeding tube* | [redacted] | [redacted] | [redacted] |
| **Motor function** | [redacted] | | |
| *HFMSE score (n=32)* | [redacted] | [redacted] | [redacted] |
| *RULM score (n=30)* | [redacted] | [redacted] | [redacted] |
| **Number of subjects who use a wheelchair** | [redacted] | [redacted] | [redacted] |
| *Yes* | [redacted] | [redacted] | [redacted] |
| *No [a]* | [redacted] | [redacted] | [redacted] |
| **Non-invasive ventilation** | [redacted] | [redacted] | [redacted] |
| **Ventilator support** | [redacted] | [redacted] | [redacted] |
| *Daily/weekly* | [redacted] | [redacted] | [redacted] |
| *Night* | [redacted] | [redacted] | [redacted] |
| *Yes (8h)* | [redacted] | [redacted] | [redacted] |
| *Other* | [redacted] | [redacted] | [redacted] |
| *Missing* | [redacted] | [redacted] | [redacted] |
| **Scoliosis, Yes/No** | [redacted] | [redacted] | [redacted] |
| **Serious respiratory events [b] (n=45)** | [redacted] | [redacted] | [redacted] |
| *events* | [redacted] | [redacted] | [redacted] |
| *Total subject months (in registry)* | [redacted] | [redacted] | [redacted] |

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; Max, maximum; Min, minimum; SD, standard deviation; SMA, spinal muscular atrophy; SMN, spinal motor neuron; RULM, Revised Upper Limb Module; V0, start treatment.
Notes: [a] In the original submission, 2 patients were indicated, subsequently confirmed to be a data entry error in the Italian registry. [b] in the 12 months prior to V0. [c] Only included patients with at least one visit before treatment and six months of follow-up after treatment initiations.

### *Outcomes (motor function)*

*Nusinersen-treated versus untreated (BSC alone) patients*

In the analysis (data cut-off: August 2020) HFMSE and RULM scores were assessed using a standard mixed model. The Standard linear mixed model was fit among both treated and untreated type III non-ambulant patients using outcome data collected after treatment initiation (for treated patients) or after the assigned index date (for untreated patients). The model estimated slopes of change over time separately in each treatment group, thus permitting assessment of whether the trajectory of the outcome over time differed between treated and untreated patients. Results were expressed as estimated change in pts/week (95% CI) and slopes were adjusted for important covariates (age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores).

A significant decrease of 0.06 points per week (i.e., 3.12 points in 12 months; P <0.0001) was observed in HFMSE score in non-ambulant type III SMA patients prior to initiation of treatment. After adjustment for the predefined confounders, there was a significant between-group difference in rate of change in HFMSE score over time in nusinersen-treated and untreated patients (P <0.0001); (Table 9).

Nusinersen-treated patients showed a significant increase of 0.02 points per week (i.e., 0.80 points in 12 months, P=0.0131), while untreated patients showed a significant decrease of 0.11 points per week (i.e., -5.67 points in 12 months, P <0.0001). This equates to an overall difference of 6.47 points over 12 months. This difference is similar to the type II patients in the randomised, placebo control trial of nusinersen (CHERISH), which showed an HFMSE 4.9 difference between the treated and non-treated groups at 15 months (Mercuri, Darras, et al., 2018).

**Table 9: HFMSE score slopes, overall cohort (nusinersen, n=159; untreated, n=9), following nusinersen initiation**

| | Beta estimate | SE | DF | T-value | Pr > \|t\| | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Slope with treatment (time in weeks)** | **0.01530** | 0.006133 | 380 | 2.49 | **0.0131** | 0.003238 | 0.02736 |
| **Slope without treatment (time in weeks)** | **-0.1090** | 0.01767 | 355 | -6.17 | **<.0001** | -0.1438 | -0.07425 |
| **Difference in slopes** | **0.1243** | 0.01871 | 358 | 6.64 | **<.0001** | 0.08751 | 0.1611 |
| DF = degrees of freedom, CI = confidence interval, SE = standard error<br>Standard mixed-effects models adjusted for age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores | | | | | | | |

A significant decrease of 0.02 points per week (i.e., 1.04 points in 12 months [P <0.0001]) was observed in RULM score in non-ambulant type III SMA patients prior to initiation of treatment.

After adjustment for the predefined confounders, there was a numerical between-group difference in rate of change in RULM score over time in nusinersen-treated and untreated patients (P=0.0976); (Table 10).

Nusinersen-treated patients showed a significant increase of 0.02 points per week (i.e., 0.92 points in 12 months [<0.001]), while untreated patients showed a decrease of 0.01 points per week (i.e. -0.47 points in 12 months). This equates to an overall difference of 1.39 points (non-significant) over 12 months. This should be benchmarked against the type II patients in the randomised, placebo control trial of nusinersen (CHERISH), which showed a difference in RULM score of 3.7 between the treated and non-treated groups at 15 months (Mercuri, Darras, et al., 2018).

**Table 10: RULM score slopes, overall cohort (nusinersen, n=159; untreated, n=9), following nusinersen initiation**

| | Beta estimate | SE | DF | T-value | Pr > \|t\| | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Nusinersen (n=159)** Slope (time in weeks) | **0.01760** | 0.005141 | 357 | 3.42 | **0.0007** | 0.007492 | 0.02771 |
| **Untreated** Slope (time in weeks) | -0.00921 | 0.01530 | 331 | -0.60 | 0.5476 | -0.03930 | 0.02088 |
| **Difference in slopes** | 0.02681 | 0.01614 | 334 | 1.66 | 0.0976 | -0.00493 | 0.05855 |
| DF = degrees of freedom, CI = confidence interval, SE = standard error<br>Standard mixed-effects models adjusted for age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores | | | | | | | |

## *Sub-cohort (n=[redacted]) analyses*

In the sub-cohort analysis (data cut-off: August 2020) HFMSE and RULM were assessed prior and post-initiation of nusinersen. Table 11 shows the average number of visits and follow-up, pre-and post-initiation of treatment, in the non-ambulant type III SMA analysis population.

**Table 11. Visits and follow-up of patients – pre- and post-nusinersen initiation (sub-cohort, n=[redacted])**

| | Pre-treatment initiation | Post-initiation |
|---|---|---|
| Visits, n (median; range) | [redacted] | [redacted] |
| Time between visits, days (median; range) | [redacted] | [redacted] |
| Follow-up, weeks (mean, ± SD) | [redacted] | [redacted] |
| Abbreviations: SD, standard deviation. | | |

The piecewise linear mixed-effects model was restricted to treated patients with data on outcomes both before and after treatment. The model estimated a pre-treatment slope as well as a change in that slope at the time of treatment initiation, thus permitting assessment of whether treatment impacted the trajectory of the outcome over time.

The HFMSE results showed that before the start of nusinersen treatment the score decreased (an average of -0.06 points per week [-3.12 points in 12 months]), which was statistically significant [p<0.0001]). Stabilisation was seen after nusinersen treatment was initiated (-0.01 points per week), equating to -0.52 points in 12 months, giving an overall difference between pre- and post-nusinersen initiation of 2.6 points

in 12 months. This change in slope, indicating stabilisation of disease, from pre- to post-nusinersen initiation was statistically significant (p=0.002) (Table 12).

**Table 12. HFMSE score slopes – pre- and post-nusinersen initiation**

| | Beta estimate | SE | DF | T-value | Pr > \|t\| | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Slope before initiation of nusinersen (time in weeks)** | -0.05637 | 0.004095 | 243 | -13.77 | <.0001 | -0.06444 | -0.0483 |
| **Slope after initiation of nusinersen (time in weeks)** | -0.01044 | 0.01251 | 243 | -0.83 | 0.4049 | -0.03509 | 0.01421 |
| **Difference in slopes** | 0.04593 | 0.01441 | 243 | 3.19 | 0.0016 | 0.01755 | 0.07431 |

DF = degrees of freedom, CI = confidence interval, SE = standard error
Standard mixed-effects models adjusted for age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores

The RULM scores showed a significant decrease in slope before initiation of nusinersen treatment (an average of -0.06 points per week [p<0.0001]), equating to -2.91 points in 12 months. Stabilisation was observed after the initiation of nusinersen (an average of 0.00 points per week [non-significant]), equating to -0.02 points in 12 months, giving an overall difference between pre- and post-nusinersen initiation of 2.91 points. The change in slope between pre- and post-treatment initiation was statistically significant (p=0.019) (**Error! Not a valid bookmark self-reference.**). The results did not change appreciably after omitting patients who were already at the maximum score at baseline (n=2) from the analysis (not shown).

**Table 13. RULM score slopes – pre- and post-nusinersen initiation**

| | Beta estimate | SE | DF | T-value | Pr > \|t\| | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Slope before initiation of nusinersen (time in weeks)** | -0.021 | 0.004019 | 233 | -5.22 | <.0001 | -0.02892 | -0.01308 |
| **Slope after initiation of nusinersen (time in weeks)** | -0.00249 | 0.005394 | 222 | -0.46 | 0.6448 | -0.01312 | 0.00814 |
| **Difference in slopes** | 0.01851 | 0.007828 | 226 | 2.36 | 0.0189 | 0.003083 | 0.03393 |
| DF = degrees of freedom, CI = confidence interval, SE = standard error<br>Standard mixed-effects models adjusted for age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores | | | | | | | |

### *Subgroup analyses (adult and paediatric subgroups)*

*Statistics*

A Standard linear mixed model was used to compare nusinersen-treated patients with untreated patients (BSC alone). A piecewise linear mixed-effects model was used to determine the slopes in Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM) scores.

*Baseline characteristics*

The baseline characteristics for the paediatric and adult subgroups from the sub-cohort are presented in

Table **14**.

**Table 14. Baseline characteristics, European registries – paediatric and adult subgroups**

| Baseline Characteristics | All (n=[redacted] | Paediatric (n=[redacted] | Adult (n=[redacted] |
|---|---|---|---|
| **Gender, M/F n (%)** | [redacted] | [redacted] | [redacted] |
| **Registry, n (%)** | | | |
| *German* | [redacted] | [redacted] | [redacted] |
| *Italian* | [redacted] | [redacted] | [redacted] |
| *Spain* | [redacted] | [redacted] | [redacted] |
| ***SMN2* copies, n (%)** | | | |
| *1* | [redacted] | [redacted] | [redacted] |
| *2* | [redacted] | [redacted] | [redacted] |
| *3* | [redacted] | [redacted] | [redacted] |
| *4* | [redacted] | [redacted] | [redacted] |
| *> 4* | [redacted] | [redacted] | [redacted] |
| *Unknown* | [redacted] | [redacted] | [redacted] |
| **Age at symptom onset, n (%)** | [redacted] | | [redacted] |
| *< 3 years* | [redacted] | [redacted] | [redacted] |
| *≥ 3 years* | [redacted] | [redacted] | [redacted] |
| **Disease duration, years**, mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |
| **Age at first dose of treatment, years**, mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |
| **Age at last dose of treatment, years,** mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |
| **Age at last follow-up, years,** mean ± SD; median (min–max) | [redacted] | [redacted] | [redacted] |
| **Number of doses,** mean ± SD; Median (min–max) | [redacted] | [redacted] | [redacted] |
| **Feeding** | | | |
| *Unsupported* | [redacted] | [redacted] | [redacted] |
| *Oral, no supplements needed* | [redacted] | [redacted] | [redacted] |
| *Oral intake solids* | [redacted] | [redacted] | [redacted] |
| *No feeding tube* | [redacted] | [redacted] | [redacted] |
| **Motor function** | | | |
| *HFMSE score, mean ± SD; Median (min–max)* | [redacted] | [redacted] | [redacted] |
| *RULM score mean ± SD; Median (min–max)* | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| **Number of subjects who use a wheelchair** | [redacted] | | [redacted] |
| *Yes (full-time/part-time), n(%)* | [redacted] | [redacted] | [redacted] |
| *No* | [redacted] | [redacted] | [redacted] |
| **Non-invasive ventilation** | [redacted] | [redacted] | [redacted] |
| **Ventilator support** | | | |
| *Daily/weekly* | [redacted] | [redacted] | [redacted] |
| *Night* | [redacted] | [redacted] | [redacted] |
| *Yes (8h)* | [redacted] | [redacted] | [redacted] |
| *Other* | [redacted] | [redacted] | [redacted] |
| **Scoliosis** | | | |
| *Yes* | [redacted] | [redacted] | [redacted] |
| *No* | [redacted] | [redacted] | [redacted] |
| **Serious respiratory events[1]** | [redacted] | [redacted] | [redacted] |
| *n (%)* | [redacted] | [redacted] | [redacted] |
| *Events* | [redacted] | [redacted] | [redacted] |
| *Total subject months (in registry)* | [redacted] | [redacted] | [redacted] |

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; Max, maximum; Min, minimum; SD, standard deviation; SMA, spinal muscular atrophy; SMN, spinal motor neuron; RULM, Revised Upper Limb Module; V0, start treatment.
Notes: [1] in the 12 months before baseline (V0) based on medical records

*Nusinersen-treated versus untreated patients*

The comparison of nusinersen-treated patients ([redacted] adults, [redacted] paediatrics) versus untreated patients (BSC alone; [redacted] adults, [redacted] paediatrics) was conducted on the full non-ambulant type III population (n=168).

In the analysis (data cut-off: August 2020) HFMSE and RULM scores were assessed using a standard linear mixed model, results were expressed as estimates changes in points/week (95% CI). In both HFMSE and RULM scores, the positive difference in slope in nusinersen-treated patients compared to the untreated patients – indicating disease stabilisation after treatment with nusinersen − was observed in both the adult and paediatric subpopulations (Table 15).

**Table 15. HFMSE and RULM scores in nusinersen-treated vs. untreated (BSC alone) adult and paediatric patients**

| | **HFMSE** estimates changes in pts/week (95% CI) | | | **RULM** estimates changes in pts/week (95% CI) | | |
|---|---|---|---|---|---|---|
| | **All** | **Paediatrics[1]** | **Adults[2]** | **All** | **Paediatrics[1]** | **Adults[2]** |
| nusinersen-treated | 0.015 (0.003–0.027) | 0.013 (−0.015–0.041) | 0.015 (0.003–0.028) | 0.018 (0.007–0.028) | 0.023 (0.006–0.040) | 0.014 (0.001–0.027) |
| Untreated | −0.109 (−0.144 to −0.074) | −0.109 (−0.156 to −0.061) | 0.012 (−0.051–0.075) | −0.009 (−0.039–0.021) | −0.009 (−0.037–0.019) | −0.013 (−0.077–0.050) |
| Notes: [1] treated vs untreated; n=37 vs n=5. [2] treated vs untreated; n=122 vs n=4<br>Standard mixed-effects models adjusted for age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores | | | | | | |

*Sub-cohort (n=[redacted]) analyses*

The HFMSE and RULM score slopes are presented in Table 16 and Table 17, respectively, for pre- and post-nusinersen initiation in the paediatric and adult subgroups from the European Registries data (Biogen data on file, 2020). The changes in slopes between pre- and post-treatment initiation for HFSME scores and RULM scores were statistically significant (HFMSE: P=0.008; RULM: P=0.009) in the paediatric subgroup.

**Table 16. HFMSE score slopes – pre- and post-nusinersen initiation in the adult and paediatric subgroups, sub-cohort (n=[redacted])**

| | Beta estimate | SE | DF | T-value | Pr > \|t\| | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Adults (n=[redacted])** | | | | | | | |
| **Slope before initiation of nusinersen (time in weeks)** | 0.01661 | 0.007938 | 141 | 2.09 | 0.0382 | 0.000915 | 0.0323 |
| **Slope after initiation of nusinersen (time in weeks)** | 0.007256 | 0.01023 | 141 | 0.71 | 0.4792 | -0.01296 | 0.02747 |
| **Difference in slopes** | -0.00935 | 0.01458 | 141 | -0.64 | 0.5222 | -0.03817 | 0.01947 |
| **Paediatrics (n=[redacted])** | | | | | | | |
| **Slope before initiation of nusinersen (time in weeks)** | -0.09906 | 0.007547 | 85 | -13.13 | <.0001 | -0.1141 | -0.08405 |
| **Slope after initiation of nusinersen (time in weeks)** | -0.03135 | 0.02081 | 85 | -1.51 | 0.1356 | -0.07272 | 0.01002 |
| **Difference in slopes** | 0.06771 | 0.02518 | 85 | 2.69 | 0.0086 | 0.01766 | 0.1178 |

DF = degrees of freedom, CI = confidence interval, SE = standard error
Standard mixed-effects models adjusted for age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores

**Table 17. RULM score slopes – pre- and post-nusinersen initiation in the adult and paediatric subgroups, sub-cohort (n=[redacted])**

| | Beta estimate | SE | DF | T-value | Pr > \|t\| | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Adults (n=[redacted])** | | | | | | | |
| **Slope before initiation of nusinersen (time in weeks)** | -0.00881 | 0.005839 | 162 | -1.51 | 0.1331 | -0.02035 | 0.002717 |
| **Slope after initiation of nusinersen (time in weeks)** | 0.001102 | 0.006161 | 152 | 0.18 | 0.8582 | -0.01107 | 0.01327 |
| **Difference in slopes** | 0.009916 | 0.009702 | 158 | 1.02 | 0.3083 | -0.00924 | 0.02908 |
| **Paediatrics (n=[redacted])** | | | | | | | |
| **Slope before initiation of nusinersen (time in weeks)** | -0.03093 | 0.005866 | 65 | -5.27 | <.0001 | -0.04265 | -0.01921 |
| **Slope after initiation of nusinersen (time in weeks)** | -0.00772 | 0.009641 | 65 | -0.8 | 0.4265 | -0.02697 | 0.01154 |
| **Difference in slopes** | 0.02322 | 0.0135 | 65 | 1.72 | 0.0903 | -0.00375 | 0.05018 |

DF = degrees of freedom, CI = confidence interval, SE = standard error
Standard mixed-effects models adjusted for age at symptom onset, sex, *SMN2* copy number, duration of disease, registry, age at baseline and baseline scores

### *Interpretation of clinical effectiveness*

This analysis using registry data from three European registries (Biogen data on file, 2020) demonstrates that treatment with nusinersen provides clinical stabilisation in non-ambulant type III patients in the real-world, compared with the continued functional decline seen in untreated (BSC only) patients in line with the established natural history of the disease.

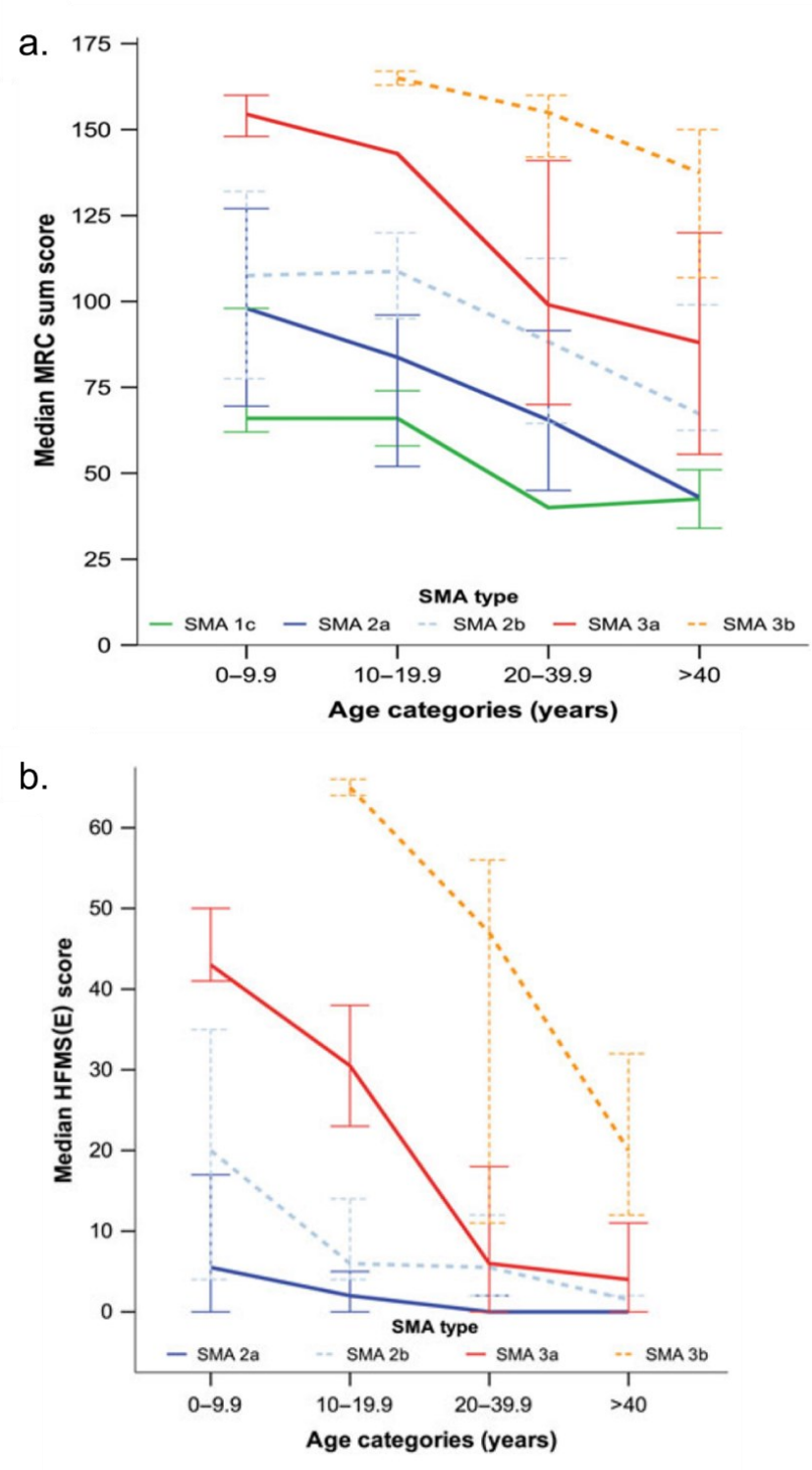
In the overall cohort (n=168), a standard mixed effects model was used to compare changes in HFMSE and RULM scores in nusinersen-treated (n=159) and untreated patients (n=9). Patients treated with nusinersen experienced a statistically significant increase in HFMSE score, while those who remained untreated continued to show a statistically significant and clinically meaningful (≥3 points; (Maggi et al., 2020)) decrease; the difference between nusinersen-treated and untreated groups was

statistically significant, and equates to an overall difference of 6.47 points over 12 months. This difference is similar to that observed in type II patients in the randomised, placebo-controlled trial of nusinersen (CHERISH), which showed an HFMSE score difference of 4.9 between the treated and non-treated groups at 15 months (Mercuri, Darras, et al., 2018).

Similarly for RULM, following the initiation of nusinersen, treated patients experienced a statistically significant increase in RULM score while those who remained untreated continued to show a decrease in RULM score, equating to an overall difference of 1.39 points (non-significant) at 12 months. This should be benchmarked against that observed in type II patients in the randomised, placebo-controlled trial of nusinersen (CHERISH), which showed a difference in RULM score of 3.7 between the treated and non-treated groups at 15 months (Mercuri, Darras, et al., 2018).

Improvements in functional outcomes were also observed in the sub-cohort (n=51) analysis, which included all enrolled individuals with non-ambulant type III SMA, who were treated with nusinersen and had ≥1 visit prior to nusinersen initiation and ≥6 months follow-up. A piecewise linear mixed-effects model was used to assess whether the treatment impacted the trajectory of the outcome over time. This showed stabilisation of HFMSE score following initiation of nusinersen, equating to an overall difference between pre- and post-nusinersen initiation of 2.6 points over 12 months, which is a trend towards a clinically meaningful improvement (≥3 points; (Maggi et al., 2020)). Thus, treatment with nusinersen enables retention of physical abilities, in contrast to the natural decline that is experienced by those who do not receive disease-modifying therapy (Figure 2) (Wadman et al., 2018). Similarly, stabilisation of RULM was observed following initiation of nusinersen, equating to an overall difference between pre- and post-nusinersen initiation of 2.91 points over 12 months, which is a clinically meaningful improvement (≥2 points; (Maggi et al., 2020)). The treatment goal of maintaining arm function was therefore achieved with nusinersen, in contrast to the natural decline that is experienced by those who do not receive disease-modifying therapy (Figure 2) (Pera et al., 2019; Wadman et al., 2018).

**Figure 2. Muscle weakness in relation to age in SMA types 1c-3b: (a) MRC scores for total upper limb strength; (b) HFMSE scores**




Abbreviations: MRC, Medical Research Council; HFMSE, Hammersmith Functional Motor Scale Expanded; SMA, spinal muscular atrophy.
Source: (Wadman et al., 2018)

Nusinersen was approved in Europe in 2017, with subsequent launch of the European registries from which data were obtained for the current analyses. The numbers of non-ambulant type III patients recruited in the registries during the relatively brief timeframe since registry launch are small (which should be considered within the context of SMA being a rare disease), and the results of the current analyses should be interpreted with caution. Nevertheless, these registry analyses provide evidence from clinical practice showing clinical stabilisation, and in some cases improvement, with nusinersen in non-ambulant type III patients, while those who are untreated show continued decline, consistent with the results of other studies in non-ambulant type III patients (Biogen Data on File, 2018; Maggi et al., 2020). Thus, this patient group benefits from treatment with nusinersen, comparable to the established benefits of nusinersen in SMA type II patients, supporting the expansion of the Managed Access Agreement to include access to nusinersen for non-ambulant type III patients. This would additionally enable further data collection in this population of high unmet need.

**Question 2**: In file ***Biogen data on file - registries. 2020*** can you please confirm that some patients included are still ambulatory? As we've read it 11 are not in wheelchairs and 11 only use them part-time. Does this mean they are ambulatory?

All 22 patients are non-ambulatory; 10 do not use a wheelchair, 11 use a wheelchair part-time, and one uses a wheelchair full-time. See Table 18 for further details of these patients.

**Table 18: Patients indicated as not using a wheelchair or using it part-time only**

| | Registry | Wheelchair user (Yes/No/PT) | Adult / paediatric | Functional ability | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Walk | Stand | Crawling | Sit | Climb |
| 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 8 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 10 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 11 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 13 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 14 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 17 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 18 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 19 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 20 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 21 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 22 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | | | | | | |

NR, not reported; PT, part-time

**Question 3**: Can you confirm the diagnoses of the patients whose PROMS data have been included as appendices?

See Table 19 for diagnoses of individual SMA patients whose data are included in the appendices.

**Table 19: Diagnosis of patients and ambulation status**

| Appendix | SMA Type | Ambulant (Yes/No)* |
|---|---|---|
| G1-32 people | 3 | 25 people (at least) are non-ambulant (out of 31 in total taking part in the survey); (see question 6 of the survey) |
| G2-Child A | 3a | No |
| G3- Child B | 3 | No |
| G4- Adult A | 3 | No |
| G4- Adult B | 3 | Yes |
| G4 Adult C | 3 | No |
| G4 Adult D | 3 | No |
| G4 Adult E | 3 | No |
| G5-34 people | 2 | No - Type 2 unable to walk |
| G5- 19 people | 3 | No |
| G11 | 2 and 3 | See appendices 1 to 5 within the document |
| H1 Child A | 3a | No |
| H1 Child B | 3a | No |
| H1 Child C | 3a | No |
| H1 Child D | 2 | No |
| H1 11yr old patient | 3 | Yes |
| H2 Sibling 1 | 3 | No |

* Based on WHO criteria for ambulation

**Question 4**: Can you provide any natural history data in relation to the trajectory of upper motor module score in untreated patients?

There is a lack of published data on the trajectory of RULM score in untreated patients. The publication by Pera et al. (Pera et al., 2019), presents longitudinal data on RULM for type II and type III SMA patients, collected within three national SMA networks across the USA, Italy and the UK. This includes 22 non-ambulant type III patients. The mean score change over 12 months in the cohort of non-ambulant type III patients was -0.23 (±2.70). Data for different age groups within this cohort are presented in Table 20.

**Table 20: Details of the cohort longitudinal data showing the RULM change (over 12 months) by age**

| Non-ambulant type III cohort | RULM Score mean change (SD) | RULM changes <-2 points | ULM changes ±2 points | RULM changes >2 points |
|---|---|---|---|---|
| All (n=22) | -0.2 (±2.7) | 18% (n:4) | 73% (n:16) | 9% (n:2) |
| 5−9 years | 1 (_2.4) | 14% (n:1) | 71% (n:5) | 14% (n:1) |
| 10-14 years (n:9) | -0.2 (_2.9) | 11% (n:1) | 78% (n:7) | 11% (n:1) |
| ≥15 years (n:6) | -1.7 (_2.4) | 33% (n:2) | 67% (n:4) | 0% (n:0) |

Source: Pera et al. (Pera et al., 2019)

Unpublished UK longitudinal data are presented from the International SMA Consortium Spinal Muscular Atrophy Patient Registry (iSMAC SMA Registry). The RULM scores are shown for individual patients for whom data are available at different ages (Figure 3) (iSMAC SMA Registry, 2021). The age at first assessment ranges from six to 16 years and age at last assessment ranges from six to 18 years, with the number of available time points per individual varying from two to six.

Overall, the data from Pera et al.(Pera et al., 2019) and iSMAC SMA Registry (iSMAC SMA Registry, 2021) are consistent with the European registry analyses showing decline in RULM score over time in non-ambulant type III patients, although there are individual variations in the trajectory.

**Figure 3. RULM score at different time points (ages) for individual non-ambulant type III patients**

## References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