




## Nusinersen efficacy data for 24-month in type 2 and 3 spinal muscular atrophy

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## Introduction

The commercial availability of nusinersen in 2017 and the subsequent approval of Onasemnogene abeparvovec and risdiplam have provided a wide therapeutic choice and the possibility to switch to a different treatment.<sup>1</sup> Even in the absence of published evidence, many families, even if partially satisfied with the results of one drug, often opt to add/switch to a different treatment with the hope to see additional efficacy.<sup>2–4</sup> This has reduced the possibility to understand long-term efficacy and safety profiles of individual drugs. There are very few long-term longitudinal data using the individual drugs and most of them are related to the long-term follow-up of clinical trial cohorts

## Abstract

The study reports real world data in type 2 and 3 SMA patients treated for at least 2 years with nusinersen. Increase in motor function was observed after 12 months and during the second year. The magnitude of change was variable across age and functional subgroup, with the largest changes observed in young patients with higher function at baseline. When compared to natural history data, the difference between study cohort and untreated patients was significant on both Hammersmith Functional Motor Scale and Revised Upper Limb Module both at 12 months and at 24 months.

in type 1 infants.<sup>5–8</sup> Less has been reported in type 2 and 3 patients.<sup>5,9,10</sup>

The aim of this study was to report on real world data in type 2 and 3 SMA patients, including children and adults, treated for at least 2 years with nusinersen and to compare them to available natural history data.

## Methods

Data were collected from the Italian centers participating to the International SMA Registry.<sup>11</sup> The study was approved by the ethics committee in each center. Written informed consent was obtained from all participants/guardians in the study.

All patients with a genetically confirmed diagnosis of SMA, a clinically confirmed diagnosis of type 2 or 3 and on treatment with nusinersen for at least 24 months were included in the study. Patients were routinely assessed using the Hammersmith Functional Motor Scale Expanded (HFMSSE)<sup>12</sup> and Revised Upper Limb Module (RULM).<sup>13</sup>

The HFMSSE consists of 33 items, investigating the ability to perform various activities.<sup>12</sup> The total score can range from 0, if all the activities are failed, to 66, if all the activities are achieved.

The RULM consists of an entry item to establish functional levels and 19 items assessing upper limb functionality.<sup>13</sup> The total score ranges from 0, if all the activities are failed, to 37, if all the activities are achieved. Measures were performed by trained clinical evaluator, training, and reliability sessions have already been reported.<sup>14</sup>

### Statistical analysis

Demographic and clinical characteristics were summarized using frequencies (percentage) for categorical variables and mean (standard deviation (SD)) or median (1st-3rd quartile) for continuous variables, unless otherwise stated. Comparisons from baseline to 12 and 24 months were done using the Wilcoxon signed-rank test. Twenty-four-month changes were also analyzed subdividing the cohort according to functional status (sitters vs. walkers), SMA type 3 subtype (3A and 3B) and according to age-bands.<sup>15–19</sup> Pearson's Correlation test was performed to measure correlation between disease duration and 24-month changes, using Cohen's conventions as interpretation.

For both measures, for which reference data from untreated patients collected using the same tools by the same evaluators with similar subgroup classification were available,<sup>18,19</sup> we used *T*-test to compare the magnitude

of changes and baseline characteristics in treated and untreated patients in relation to age.

### Results

The cohort included 46 SMA type 2 (age range: 2.64–47.82 years) and 65 SMA type 3 patients (age range: 3.21–68.27 years), all treatment naïve at baseline. The mean duration of follow-up was 2.56 years. Table 1 describes baseline characteristics and demographics of the cohort.

All 111 patients performed HFMSSE at baseline and after 12 and 24 months, and 80 also performed the RULM in the same visits. In many recent cases clinical follow-up visits were missed because of COVID-19 pandemic.

Table 2 shows results of the scores at baseline, 12 and 24 months.

### HFMSSE

There was a significant increase between baseline and 12-month in type 2 patients ( $p = 0.009$ ) but not in type 3 patients ( $p = 0.130$ ). The increase between baseline and 24 months was significant in both type 2 and 3 patients ( $p = 0.019$ ;  $p = 0.017$ ). The results were confirmed when excluding patients with maximum score at baseline ( $n = 1$ ). When subdivided into age subgroups the difference at 24 months was significant for the subgroup <5 years in both type 2 ( $p = 0.009$ ) and type 3 patients ( $p = 0.043$ ), but not in the older subgroups. Supplementary Figures S1 and S2 show individual changes in SMA 2 and 3 subdivided by age-bands.

In type 2 patients the 24-month increase was significant in sitters ( $p = 0.020$ ) but not in non-sitters ( $p = 0.577$ ). In type 3 patients the 24-month increase was significant in ambulant ( $p = 0.004$ ) but not in non-ambulant

**Table 1.** Baseline characteristics and demographics of the cohort subdivided by SMA type.

	ALL	SMA 2	SMA 3
N	111	46	65
Sex, n (%)			
Male	60 (54.05)	25 (54.35)	35 (53.85)
Female	51 (45.95)	21 (45.65)	30 (46.15)
Age at baseline (years), median (1st-3rd quartile)	12.51 (6.12–25.79)	6.66 (3.89–12.23)	17.86 (11.23–39.87)
Age < 18 years, n (%)	73 (65.77)	40 (86.96)	33 (50.77)
Median age in pediatric population (1st-3rd quartile), years	7.86 (4.66–12.32)	5.94 (3.62–10.48)	11.23 (6.44–13.93)
SMA function, n (%)			
Non-sitter	9 (28.11)	8 (17.39)	1 (1.54)
Sitter	61 (54.95)	38 (82.61)	23 (35.38)
Walker	41 (36.94)	0 (0.00)	41 (63.08)
Baseline HFMSSE score, median (1st-3rd quartile)	24 (9.5–46)	8.5 (3–16)	43 (26–52)
	N = 111	N = 111	N = 111
Baseline RULM score, median (1st-3rd quartile)	28.5 (16.75–36)	15.5 (11–18.75)	35 (28–37)
	N = 80	N = 80	N = 80



( $p = 0.948$ ). When subdivided into 3A and 3B subtypes, the increase in scores was not significant in 3B patients ( $p = 0.265$ ) and showed only a trend of significance in 3A ( $p = 0.05$ ). There was a strong correlation between disease duration and 24 months changes in both SMA 2 and SMA 3 aged <5 years ( $r = -0.720$ ;  $r = -0.507$ ), and a moderate correlation in SMA 3 aged 8–14 ( $r = -0.398$ ), while it was small in the older groups ( $r \pm 0.10$ ).

## RULM

In type 2 patients, there was a significant increase between baseline and 12 months ( $p = 0.017$ ) and between baseline and 24 months ( $p = 0.018$ ). In type 3 patients, the increase was not significant at any time interval ( $p > 0.05$ ) (Table 2). The result was confirmed when excluding patients with maximum score at baseline ( $n = 18$ ). When subdivided into age subgroups the difference was not significant in any of the subgroups. Supplementary Figures S1 and S2 show individual changes in SMA 2 and 3 subdivided by age-bands.

In type 2 patients the 24-month changes were significant in sitters ( $p = 0.036$ ) but not in non-sitters ( $p = 0.276$ ). In type 3 patients the 24-month changes were not significant in both ambulant ( $p = 0.664$ ) and non-ambulant ( $p = 0.681$ ). The increase was not

significant in both 3A and 3B subtypes ( $p = 0.937$  and  $p = 1.000$ ). There was a small correlation between disease duration and 24 months changes in SMA 2 and SMA 3 in all age subgroups ( $r \pm 0.10$ ).

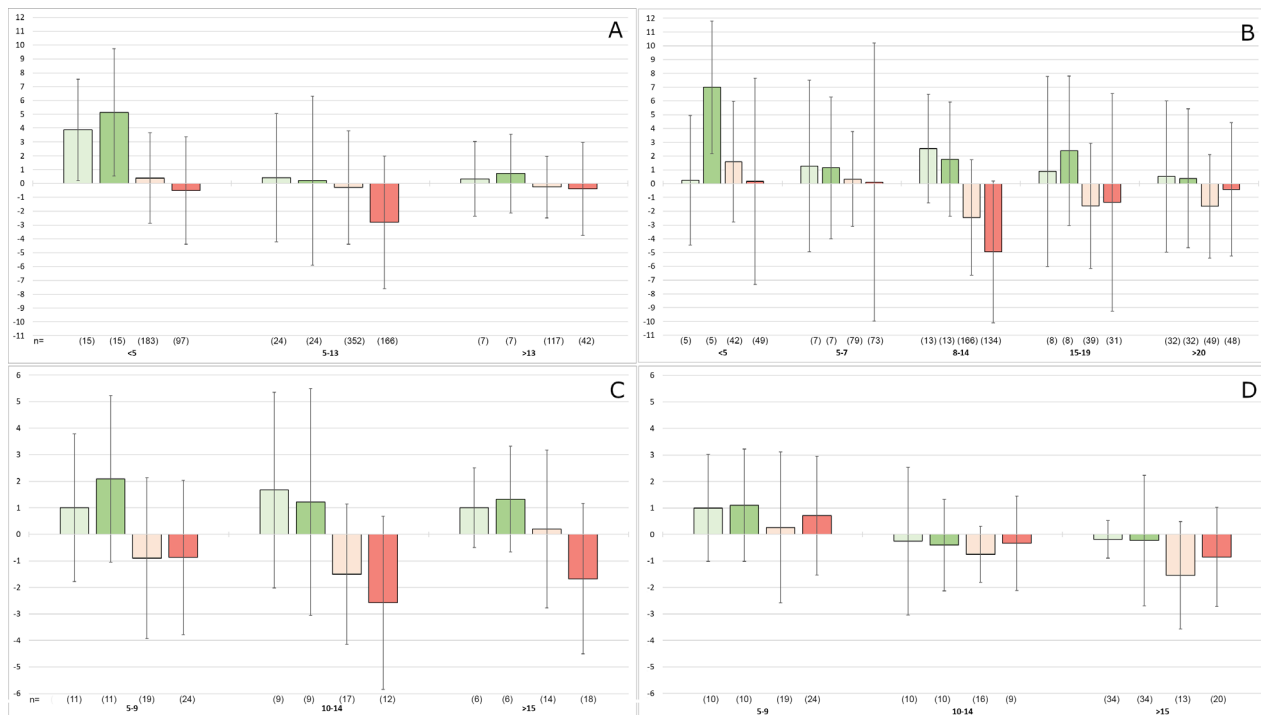
## Comparison with untreated patients

### SMA 2

When comparing treated and untreated type 2 patients there was no difference for age or HFMSE/RULM score at baseline ( $p > 0.05$ ). The difference between treated and untreated patients was significant on both HFMSE and RULM both at 12 months ( $p < 0.001$ ,  $p = 0.008$ ) and at 24 months ( $p < 0.001$ ,  $p < 0.001$ ) (Figure 1).

### SMA 3

When comparing treated and untreated type 3 patients there was no difference for age or HFMSE/RULM score at baseline ( $p > 0.05$ ), with the exception of age distribution in patients older than 20 years ( $p < 0.001$ ). The difference between treated and untreated patients was significant on both HFMSE and RULM at 12 months ( $p = 0.0002$ ,  $p < 0.001$ ). At 24 months the difference was significant on HFMSE ( $p = 0.0002$ ) but not on RULM ( $p = 0.9225$ ) (Figure 1).



**Figure 1.** Mean changes at 12 and 24 months subdivided by age groups. Key to figure: Panel A = HFMSE in SMA 2, Panel B = HFMSE in SMA 3, Panel C = RULM in SMA 2, Panel D = RULM in SMA 3. Light green = 12 months changes in treated patients, Dark green = 24 months changes in treated patients, Light red = 12 months changes in untreated patients, Dark red = 24 months changes in untreated patients.

## Discussion

Our results confirm the previously reported increase in motor function after 12 months of nusinersen treatment<sup>5,7,9,10,20</sup> but also show that further improvement, even if smaller, can also be observed in the second year. The increase was more obvious on the HFMSE, with changes reaching significance already after 12 months in type 2. In type 3 patients the changes were not significant at 12 months but became significant after 24 months. The smallest changes were observed in patients at the severe end of spectrum of both type 2 and 3.

The changes were less obvious on the RULM even if they reached significance in type 2 patients. This difference may be partly explained by the ceiling effect frequently found in ambulant three patients in whom the HFMSE was more sensitive to detect changes. In contrast, the RULM was better suited than the HFMSE to detect changes in older type 2 patients at the time when they have reached very low scores on the HFMSE. Further information on ambulant patients may have been obtained by using the 6MWT, as previously reported,<sup>5</sup> but this was unfortunately not systematically performed in all centers.

Although there was an improvement between baseline and 24 months in the overall cohort, this appeared to be mainly driven by the younger cohort as the mean improvements were smaller in the other age subgroups. The advantage of the present study is that we not only had a much larger cohort of treated patients, but also a suitable large comparator group of untreated patients in different age subgroups available from recent natural history studies.<sup>18–22</sup> The comparison was possible because both treated and natural history cohorts had been assessed by the same clinical evaluators using the same measures.

The comparison showed a consistent difference between treated and untreated patients. This held true not only in the age subgroups in whom there was the most obvious therapeutic response, such as type 2 younger than 5 years, but also in those subgroups in whom there was an apparent small change after treatment that became meaningful when compared to the marked decline found in the untreated patients of the same age and functional level.

In conclusion, our study confirms that an improvement in nusinersen-treated patients can also be observed in the second year, as suggested by the follow-up of clinical trials<sup>5</sup> or in smaller cohorts of treated patients.<sup>9,10</sup> Our study also strongly suggests that comparison with available natural history data in untreated patients can therefore help to set up correct expectations and to better identify responders in patients of different age and functional level. As a number of patients are considering

switching to a new drug after 1 year of treatment, our longitudinal 24-month data using monotherapy with nusinersen will help to better understand possible differences with the changes observed following the introduction of a new or concomitant drug.

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## Author contributions

MP,GC, MCP, and EM have contributed in conception and design of the study. GC, MCP, VAS, SM, AdA, CB, FS, EA, RDS, MS, VDB, SM, CP, ALF, LA, AC, MC, AL, MR, CC, AP, CB, MP, NB, and EB have contributed in the acquisition and analysis of data. MP, GC, MCP, CB, ALF, LA, AC, MR, CC, EB, and EM have contributed in drafting the manuscript. The composition of the Italian ISMAC group is listed in the supplementary file 1.

## Conflict of Interest

MCP, GC, VAS, SM, ADA, CB, FS, EA, RDS, EB, MP, and EM have been consultant for BIOGEN S.R.L. which owns patent rights to nusinersen that was used in this study.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1**

**Figure S2**

**Data S1**