# Nusinersen in Type 1 Spinal Muscular Atrophy: Twelve-Month Real-World Data

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on behalf of the Italian Expanded Access Program Working Group

**Objective:** The aim of the study was to report 12-month changes after treatment with nusinersen in a cohort of 85 type I spinal muscular atrophy patients of ages ranging from 2 months to 15 years and 11 months.
**Methods:** All patients were assessed using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and the Hammersmith Infant Neurological Examination-Section 2 (HINE-2).
**Results:** Two of the 85 patients had 1 *SMN2* copy, 61 had 2 copies, and 18 had 3 copies. In 4 patients the *SMN2* copy number was not available. At baseline, the mean CHOP INTEND scores ranged between 0 and 52 (mean = 15.66, standard deviation [SD] = ±13.48), and the mean HINE-2 score was between 0 and 5 (mean = 0.69, SD = ±1.23). There was a difference between baseline and the 12-month scores on both the CHOP INTEND and the HINE-2 for the whole group ($p < 0.001$), the subgroups with 2 *SMN2* copies ($p < 0.001$), and those with 3 *SMN2* copies ($p < 0.001$). The difference was found not only in patients younger than 210 days at baseline ($p < 0.001$) but also in those younger than 5 years on the CHOP INTEND and younger than 2 years on the HINE-2.
**Interpretation:** Our results, expanding the age range and the severity of type I patients treated with nusinersen over 1 year, provide additional data on the range of efficacy of the drug that will be helpful in making an informed decision on whether to start treatment in patients of different ages and severity.

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Spinal muscular atrophy (SMA) is a rare neuromuscular disorder caused by mutations in the survival motor neuron 1 (*SMN1*) gene. In the last few years there has been an increasing number of therapeutic approaches in clinical trials. Following 2 pivotal sham, controlled, double-blind studies in the infantile and late onset form of SMA, nusinersen was

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recently approved in several countries worldwide[1,2] and was subsequently made available for all type I patients as part of an Expanded Access Program (EAP).[3] This has been an opportunity to assess the efficacy of the drug in a real-world setting in a large number of type I patients with a much wider spectrum of age[3] than those enrolled in the ENDEAR (A Phase 3, Randomized, Double-Blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients With Infantile-onset Spinal Muscular Atrophy) study, which only included patients below the age of 7 months and excluded patients with severe neonatal onset and with 3 survival motor neuron 2 *(SMN2)* copies. There has been concern that the drug may not show similar efficacy in older patients or in those with a more severe phenotype who were not included in the pivotal study.

The recently published preliminary data in an Italian cohort and in other European countries[4–8] showed promising results even in older infants and children. This was, however, mostly limited to the initial response in the first 6 months of treatment. A number of questions, such as the long-term efficacy in relation to the severity of the phenotype or to the *SMN2* copy number, have not been fully addressed.

The aim of our study was to report the 12-month follow-up, with a duration similar to the ENDEAR study, in a cohort of type I patients with a much wider range of age, severity, and *SMN2* copy numbers than those selected for the ENDEAR study.

More specifically, we wished (1) to establish if the data in the infants assessed below the age of 7 months (210 days) were consistent with the ENDEAR study; (2) to assess whether there was any improvement in older children and, if present, if this was related to age, severity, or number of *SMN2* copies; and (3) to determine if longer follow-up would help to better define the magnitude of changes. Finally, we also aimed to establish, using dedicated patient-reported questionnaires, whether possible improvements on the functional scales were related to the caregivers' perception of clinically meaningful improvements.

## Patients and Methods

Patients were initially included in the study following a nationwide search of patients with type I SMA. The details of the EAP approach in Italy have already been reported.[3] As part of the EAP, before nusinersen became commercially available, the patients had access to the treatment only in the 5 Italian centers previously involved in nusinersen trials. The results of the first 6 months have recently been published.[3]

Of the 104 SMA I patients followed up in the first 6 months of the EAP, 100 agreed to continue to be treated, whereas the other 4 decided to interrupt the treatment. Of the 4 who decided to interrupt the treatment in 2 it was because the results did not meet their expectations, in 1 because of the burden related to the procedure and of traveling, and in 1 because of the onset of a concomitant disease unrelated to SMA or to the treatment. Of the remaining 100, 4 died, 1 failed a recent scheduled appointment because of intercurrent illness, and 26 moved to other centers, as in the last year nusinersen has become commercially available and could be administered in other centers. Twelve of the 26 moved to 3 centers (Turin, Trieste, Milan), where the physiotherapist had been fully trained by the original participating centers as part of a new prospective study. Data from these centers were considered to be reliable and were therefore included in our follow-up study. Data from the remaining 14 patients followed in other centers were not included. This resulted in 81 patients with a full 12-month follow-up. Four additional patients who were not reported at 6 months because they were too young at that time had also completed the 12-month assessments and were included, resulting in a final cohort of 85 patients.

The study was approved by the institutional review board (ethics committee) in each center. Written informed consent was obtained from all participants (or guardians of participants) in the study (consent for research). All patients were assessed using both the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND),[9,10] which includes 16 items with a total score between 0 and 64, and the developmental section of the Hammersmith Infant Neurological Examination (HINE-2), which includes 8 selected motor items scored accordingly to the gradient of normal maturation.[11]

Measures were performed by clinical evaluators after training and reliability sessions.[6] The assessments were always performed after 12 months from the first dose of nusinersen, between the 6th dose of nusinersen and before the 7th dose, generally performed at 14 months. Data on nutritional and respiratory support were also noted.

### *Parent-Reported Questionnaires*

A questionnaire was developed and administered to parent/caregiver to identify their perception on whether there had been any change that was clinically meaningful to them after 1 year of treatment. At the end of the questionnaire, which included details of specific activities with open and closed questions (analysis in progress), there was a final section with 3 questions asking the parent/caregiver to report: (1) if there had been any change in general function:

(a) stable, (b) improved, (c) deteriorated; (2) if there was an improvement, to clarify whether this was mainly related to (a) respiratory, (b) motor function, (c) swallowing and speech; and (3) if there was a deterioration, to clarify whether this was mainly related to (a) respiratory, (b) motor function, (c) swallowing and speech.

The survey was carried out in all the centers. At the time of completing the questionnaire, the families were not informed of the results of the functional assessments.

### Statistical Analysis

The cohort was stratified according to the criteria used in the 6-month follow-up study.[6] This included subdividing them according to the copy number, to the age when they started treatment, and to the severity of the disease. The cohort was subdivided using the Dubowitz decimal classification,[12] classifying as 1.1 the infants at the more severe end of the spectrum, with severely reduced mobility at birth and early respiratory and bulbar difficulties; as 1.5 as those with the most common phenotype in type I SMA, with inability to raise the legs against gravity or maintain the head posture but having, at diagnosis, no difficulty with feeding and swallowing, and no obvious respiratory distress; and as 1.9 the mildest phenotypes, often diagnosed after the first few months, with the ability to achieve some head control and have less respiratory compromise.

Variables were described by mean and standard deviation (SD). Paired sample *t* test or repeated measures analysis of variance (ANOVA) were used to compare the mean score of both the CHOP INTEND and HINE-2, between baseline and 12-month follow-up. The Spearman test was used to measure the correlation between nonparametric variables.

Two separate multiple linear regression model were performed to predict the response to treatment. There were 2 response variables: the first was the difference between the CHOP INTEND score at 12 months and the CHOP INTEND score at baseline, and the second was the difference between HINE-2 score at 12 months and HINE-2 score at baseline.

The following variables were included in both regression models as predictors: age at start of treatment, score at baseline, severity of diseases type, and *SMN2* copy number. Version 23 of the SPSS software (IBM, Armonk, NY) was used for all statistical analyses, setting the significance at $p < 0.05$.

## Results

The final cohort included 85 patients with full 12-month assessments. Their ages ranged from 2 months to 15 years and 11 month (mean = 4.70; SD = ±4.21). Two patients had 1 *SMN2* copy, 61 had 2 copies and 18 had 3 copies. In 4 patients the *SMN2* copy number was not available. In agreement with the Dubowitz decimal classification,[12] in our cohort 8 of the 85 were classified as 1.1, 48 as 1.5, and 29 as 1.9.

### CHOP INTEND

At baseline, the CHOP INTEND scores ranged between 0 and 52 (mean = 15.66, SD = ±13.48).

After 12 months the scores ranged between 0 and 64 (mean = 21.14, SD = ±18.23) (Supplementary table 1).

The 12-month changes ranged between −6 and 32 (mean = 5.48, SD = ±7.62). Twelve patients (14.11%) showed negative changes between −1 and − 6 (mean = −2, SD = ±1.47). Another 20 (23.52%) remained stable or had a 1-point improvement. Of the remaining 53 (62.35%), 9 improved 2 points, 44 > 2 points, and 38 ≥ 4 points (Fig 1).

### HINE-2

At baseline, the HINE-2 scores ranged between 0 and 5 (mean = 0.69, SD = ±1.23). At 12 months the scores ranged between 0 and 16 (mean = 2.16, SD = ±3.58) (Supplementary table 1). The 12-month changes ranged between −3 and 12 (mean = 1.34, SD = ±2.90). Four patients (4.70%) showed negative changes. Fifty-three (62.35%) remained stable, 7 had 1-point improvement (8.23%), 5 (5.88%) improved 2 points, and 16 (18.82%) improved more than 2 points. Improvements were observed in the items assessing head control and sitting, with 16 patients achieving sitting independently. An additional patient, classified as 1.9 and treated at 8 months, achieved standing.

Of the 16 infants who achieved a full score for sitting on the HINE-2, 8 were classified as 1.5 and 8 as 1.9. Seven of the 8 classified as 1.5 were treated within 7 months of age and 1 between 6 and 24 months (10 months). Three of the 8 classified as 1.9 were treated within 7 months and the other 5 between 6 and 24 months (11, 9, 8, respectively).

### Statistical Analysis

Using a paired *t* test, there was a significant difference between baseline and 12-month scores on both the CHOP INTEND and the HINE-2 for the whole group ($p < 0.001$). The multiple regression models show that the independent variables included in the model (age at baseline, baseline score, *SMN2* copy numbers, and severity of disease) predict CHOP INTEND changes ($p < 0.0005$) and HINE-2 scores changes ($p < 0.0005$) after 12 months of treatment.

On the CHOP INTEND, the multiple correlation coefficient is $R = 0.938$; $R^2$ for overall model was 93.8%, with an adjusted $R^2 = 87.9\%$ (87.9% of the dependent variable variance is explainable by the independent variables). Copy numbers and CHOP INTEND baseline

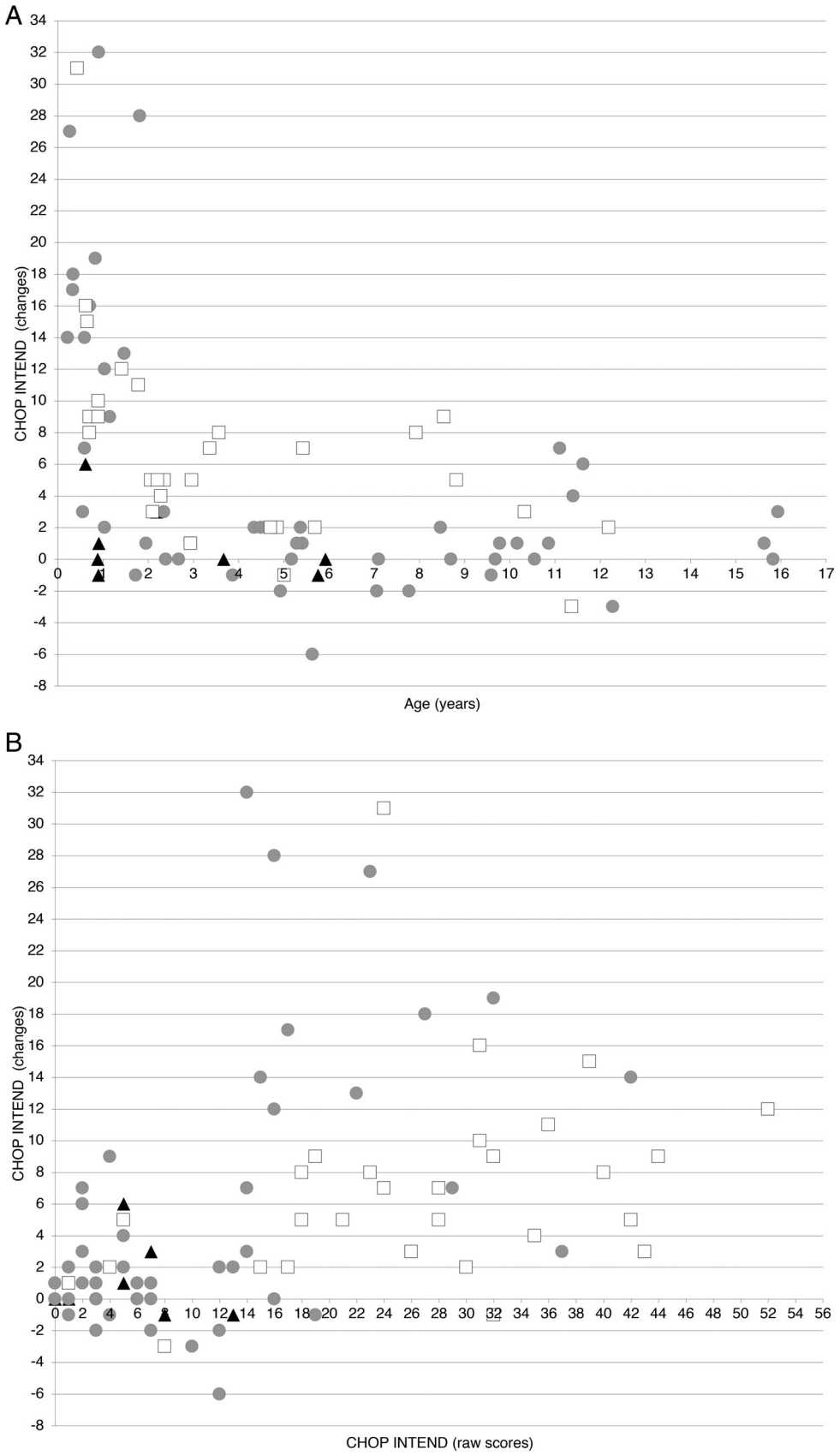


**FIGURE 1: Individual details of the CHOP INTEND changes according to severity, graded according to the Dubowitz classification, age (A), and baseline (B) values. Black triangle: 1.1 (n = 8), black circle: 1.5 (n = 48), square: 1.9 (n = 29). CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.**

**TABLE 1. Summary of Regression Analyses for Variables Predicting CHOP INTEND and HINE-2 Change**

| | CHOP INTEND | | | | HINE-2 | | | |
|---|---|---|---|---|---|---|---|---|
| | B | *p* | Standard Error | Standardized B Coefficients | B | *p* | Standard Error | Standardized B Coefficients |
| Constant | 8.241 | 0.001 | 2.222 | | 2.556 | 0.000 | 0.593 | |
| Severity of disease | −5.719 | 0.045[a] | 2.842 | −0.215 | −1.697 | 0.049[a] | 1.070 | −0.166 |
| Copy numbers | −1.375 | 0.512 | 2.087 | −0.076 | −0.103 | 0.894 | 0.773 | −0.015 |
| Age at baseline | −0.766 | 0.002[a] | 0.240 | −0.400 | −0.301 | 0.000[a] | 0.077 | −0.409 |
| Baseline score | 0.145 | 0.123 | 0.093 | 0.256 | 0.629 | 0.060 | 0.329 | 0.267 |
| Overall model | $R^2 = 0.879$, $F_{5,71} = 6.609$, $p < 0.0005$ | | | | $R^2 = 0.537$, $F_{5,71} = 6.120$, $p < 0.0005$ | | | |

Results of the 2 multiple linear regression models.
[a]Significant *p* values, indicating the variables that predict the response variable.
CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 = Hammersmith Infant Neurological Examination–Section 2.

score did not give a statistically significant contribution to the dependent variable. Age at baseline had a higher impact than other variables by comparing the standardized coefficients.

On the HINE-2, the multiple correlation coefficient is $R = 0.733$; $R^2$ for overall model was 53.7%, with an adjusted $R^2 = 50.2\%$ (50.2% of the dependent variable variance is explainable by the independent variables). Copy numbers and HINE-2 baseline score did not give a statistically significant contribution to the dependent variable. Age at baseline had a higher impact than other variables by comparing the standardized coefficients. Table 1 shows details of the multiple correlations.

### Nutritional Support

At baseline, 42 of 85 infants had a gastrostomy inserted or planned in the near future; 7 additional children required gastrostomy between baseline and 12 months. More accurate details on nasogastric tube or swallowing abnormalities are being collected and will be described separately.

### Respiratory Support

At baseline, 50 were on spontaneous breathing, 8 used noninvasive ventilation <10 hours, 19 used noninvasive ventilation >10 hours, and 8 had a tracheostomy. At the last follow-up, 20 required longer use of noninvasive ventilation, and tracheostomy was needed in another 2. Two patients showed a reduction in the number of hours on noninvasive ventilation. A more detailed analysis of the respiratory findings is in progress and will be reported separately.

### Twelve-Month Changes and Severity

Using a paired *t* test, there was a significant difference between baseline and 12-month scores on both the CHOP INTEND and the HINE-2 for the 1.5 ($p < 0.001$) and 1.9 ($p < 0.001$) subgroups but not for the 1.1 subgroup ($p > 0.05$). Supplementary table 1 and Figure 2 report data from the CHOP INTEND and the HINE-2 at different time points.

On the ANOVA test, there was a difference between the 3 severity subgroups on both the CHOP INTEND and HINE-2 ($p < 0.001$). There was a progressive number of patients improving more than 2 points with decreasing severity. Figure 2A and C show details of the changes in CHOP INTEND scores in the 3 subgroups. Figure 2B and D show details of the changes in HINE-2 scores in the 3 subgroups.

### Twelve-Month Changes and SMN2 Copy Number

Figure 3 shows the CHOP INTEND and HINE-2 progression from baseline to 12 months for SMA patients subdivided by *SMN2* copy number. There was a significant difference between baseline and 12 months on the CHOP INTEND for both the patients with 2 *SMN2* copies ($p < 0.001$) and for those with 3 *SMN2* copies ($p < 0.001$). Significant difference was also found between baseline and 12 months on the HINE-2 for both the patients with 2 *SMN2* copies ($p = 0.002$) and for those with 3 *SMN2* copies ($p = 0.012$).

### Twelve-Month Changes and Age at Start of Treatment

Of the 85 patients, 6 were younger than 210 days, 23 were younger than 2 years, 20 were between 2 years and 4 years

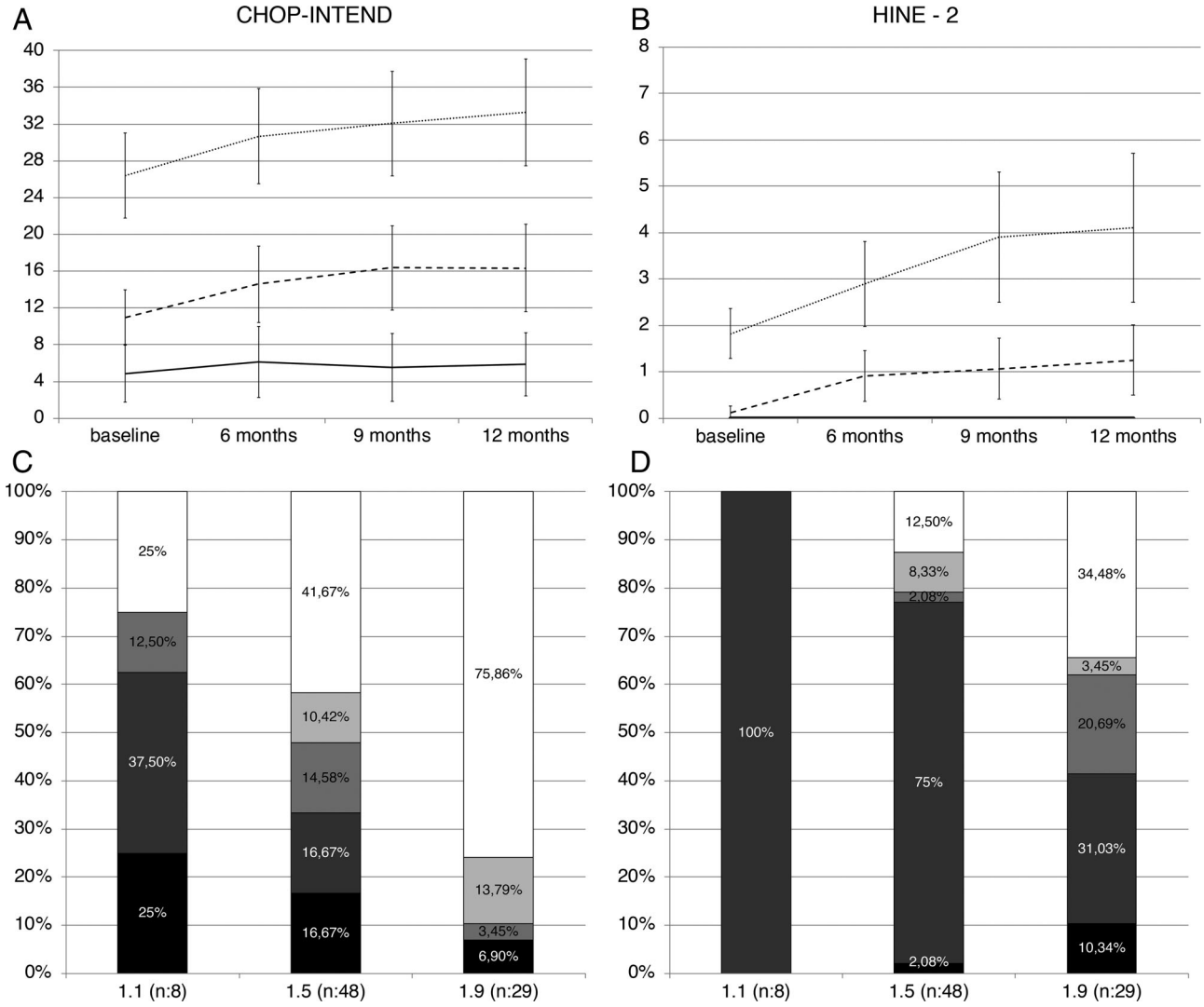


**FIGURE 2: (A, B) CHOP INTEND and HINE-2 longitudinal data on the cohort subdivided by decimal classification. Error bars represents 95% confidence intervals. Solid line: SMA type 1.1 (n = 8); dashed line: SMA type 1.5 (n = 48); dotted line: SMA type 1.9 (n = 29). (C, D) CHOP INTEND and HINE-2 score changes description on the cohort subdivided by decimal classification. From lightest to darkest, shading represents: score > 2, score = 2, score = 1, score = 0, score < 0. CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 = Hammersmith Infant Neurological Examination-Section 2.**

11 months, 29 were between 5 and 11 years 11 months, and 5 were aged above 12 years. Figure 3 shows details of the changes in scores in different age subgroups. There was a difference between baseline and 12 months on the CHOP INTEND in patients younger than 5 years (younger than 210 days, $p = 0.006$; younger than 2 years, $p = 0.001$; between 2 and 4 years, $p = 0.001$) but not in those older than 5 years (between 5 and 12 years, $p = 0.576$; older than 12 years, $p = 0.763$). There was a significant difference between baseline and 12 months on the HINE-2 in patients younger than 2 years (younger than 210 days, $p = 0.011$; younger than 2 years, $p = 0.001$) but not in those older than 2 years (between 2 and 4 years, $p = 0.226$; between 5 and 12 years, $p = 0.791$; older than 10 years, $p = 1$).

### *Parent/Patient-Reported Questionnaires*

On the 72 questionnaires completed by caregivers of patients followed in the 5 centers who participated to the survey, no one reported a decrease in function, 11 reported an overall stability, and 61 reported a general increase in function. Fifty-three out of 61 reported that the overall perception of improvement was mainly related to an improvement in motor function (85.24%), whereas the remaining 8 (13.11%) reported that the improvement was due to a combination of factors including motor, respiratory, and swallowing.

The mean changes on the CHOP INTEND were 1.45 (SD = ±2.84) in the 11 patients in whom an overall stability was reported, and 6.49 (SD = ±8.28) in the

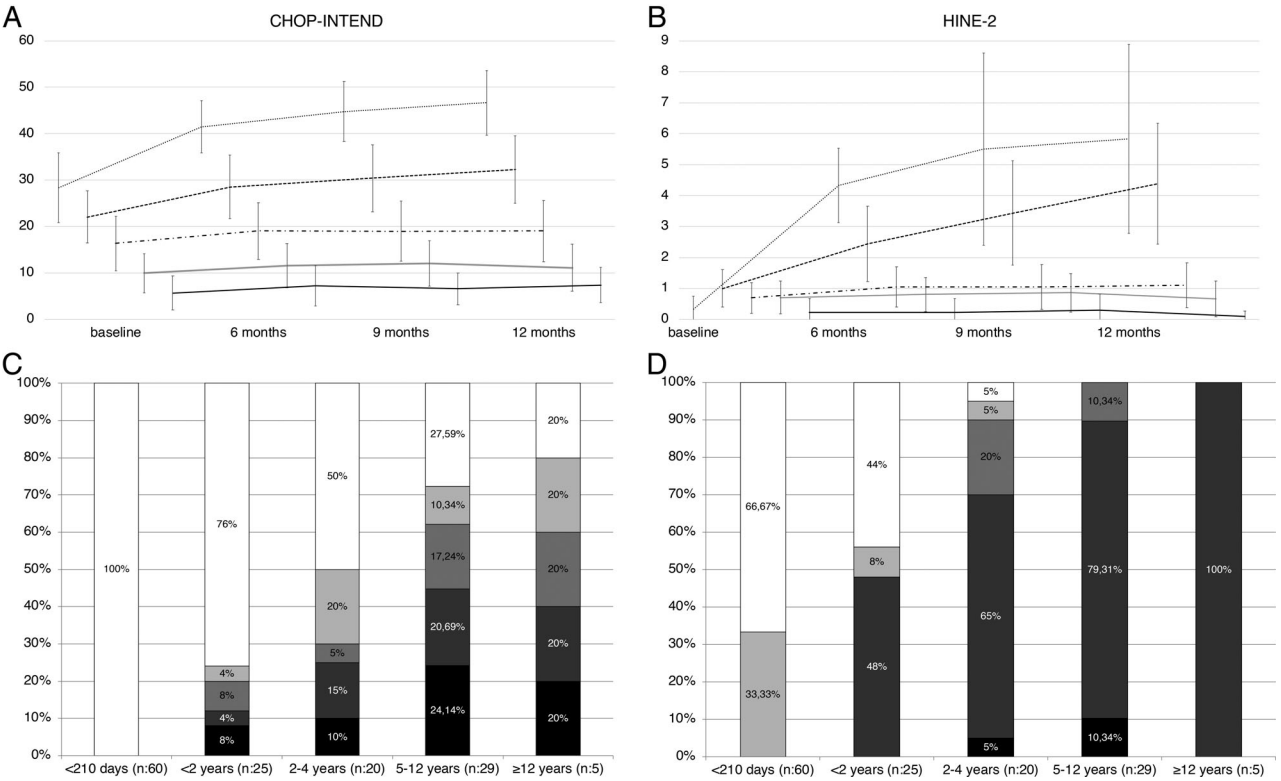


**FIGURE 3: (A, B) CHOP INTEND and HINE-2 longitudinal data on the cohort subdivided by age bands. Error bars represents 95% confidence intervals. Solid black line: <210 days (n = 6); solid gray line: <2 years (n = 25); dashed and dotted line: 2 to 4 years (n = 20); dashed line: 5 to 12 years (n = 29); dotted gray line: ≥12 years (n = 5). (C, D) CHOP INTEND and HINE-2 score changes description on the cohort subdivided by age bands. From lightest to darkest, shading represents: score > 2, score = 2, score = 1, score = 0, score < 0.**

53 in whom an overall improvement was reported. The Spearman test evidenced a correlation between CHOP INTEND score changes and answers on the parents' questionnaires ($p$ = 0.024).

## Discussion

The regulatory approval of nusinersen after 2 pivotal trials in infants and young children has been followed by different modalities of access to the drug in different countries. Although some have granted access to the drug only in type I infants, with the same criteria used in the ENDEAR clinical trial, others have granted a much wider label including all types of SMA at all ages. This has raised some concern, especially in type I SMA, that older children may have lost the therapeutic window and show little or no response to treatment.[5]

Furthermore, the possibility of administering the drug in a large number of centers in each country increases the difficulties in getting reliable assessments by trained physical therapists and sharing data. Our experience of the EAP in Italy provided the opportunity to collect prospective longitudinal data in a large cohort of patients with a much wider range of age and severity than those included in the ENDEAR study, while retaining a structured trial-like approach sharing measures, training, and reliability sessions among the centers involved in the data collection. Our results show that despite the wide age and severity range, after 12 months of treatment (6 infusions), there was a mean improvement on the CHOP INTEND of 5.46 points.

It is of note that <15% of the 85 patients had negative changes, and half of them had lost only 1 point. This is different from what was reported in untreated infants and children in natural history studies.[13–16] In contrast, over 60% of the 84 patients improved 2 points, and over 50% improved more than 2 points. The improvements on their CHOP INTEND were more obvious after 6 months, but a further smaller increase was also found between 6 and 12 months.

The magnitude of changes were smaller on the HINE-2, with 25% improving at least 2 points but also with a steady mild increase between 6 and 12 months, suggesting that achieving even partial milestones may be a more complex task, especially in older patients, and may take longer than showing an improvement on the items of the functional scale. As expected, on both measures the changes were more obvious in the infants below 7 months of age. The overall results in age group show a clear trend

of improvement on both the CHOP INTEND and HINE-2 that is different from the negative changes observed in the untreated group in the ENDEAR study[1] and in the recent natural history studies.[15,16]

An improvement was, however, also found in the infants treated between 7 and 24 months on both scales, and some improvement could also be found in the older children on the CHOP INTEND. Other factors also appeared to be important in determining the possibility of an improvement. The level of increase partly reflected the severity of the phenotype.

In our study, we did not have any patients with the most severe phenotype with prenatal onset, labeled as type 0,[17] but we included infants with the very severe phenotype with early onset, classified as 1.1[12,15] or IA.[18] These were excluded by the ENDEAR study because they were thought to be too severe and with too small residual motoneuron activity to be compatible with possible functional improvements. The overall difference between baseline and 12 months was not significant for this subgroup even though some improvement (1, 3, and 5 points, respectively) could be noted in 3 of the 5 severely affected infants treated below the age of 2 years. In contrast, the overall difference between baseline and 12 months was significant for the more common (1.5) and the mildest phenotypes (1.9).

The 12-month results in patients with 3 *SMN2* copies expand the findings reported in the ENDEAR study,[1] which only included infants with 2 *SMN2* copy numbers. Both subgroups with 2 and 3 copies showed a difference between baseline and 12 months ($p < 0.001$).

Our results, therefore, confirm the improvement observed after 6 months of treatment and provide evidence, as observed in the ENDEAR study, that further improvement can be observed between 6 and 12 months on both measures. The longer duration of the follow-up also allowed reduction of the risk that the initial response may be due to a placebo effect that is more frequent in the first months after treatment.

Previous studies have reported electrophysiological evidence of extremely reduced motoneuron activity after the first months in type I SMA[19] and have also suggested that in type I SMA, the therapeutic window can be hypothesized to be, optimally, within 1 month of age to have a motor function response within the first 3 to 6 months of age.[20] As also recently suggested by other studies,[4–8] our results provide further evidence that the therapeutic window may be larger than what was expected. Our results, expanding the age range and the severity of type I patients treated with nusinersen, provide additional data that will be helpful for other physicians and families to make an informed decision on whether to start treatment depending on the clinical and genetic features.

At the time the drug became commercially available for all SMA patients in our country, it has been difficult to counsel the families of patients who were older and more severe than those reported in the ENDEAR study, as we could only report data from the pivotal study. Our attitude was to be very cautious on not creating high expectations. In our experience, with the exceptions of the few patients with the severe phenotype treated after the first 2 years, some improvement, even if limited to very few points, was often observed in the older patients with the nonsevere phenotype at onset. These results are promising and are consistent with what the families have reported to be clinically meaningful,[21] but should be integrated with other measures assessing care burden and other aspects of activities of daily living.

Unfortunately, at the time the EAP started, because of limited funding and the large number of patients followed in each center, it was not feasible to consistently perform compound muscle action potential or motor unit number estimation to have objective measurements of the residual motoneuron activity at baseline and possible changes over time, or to use recent biomarkers like phosphorylated neurofilament heavy chain[22] that may have helped to better understand the mechanisms underlying the changes observed in our cohort. Following the commercial availability of nusinersen, there has been discussion on whether such small changes observed in some patients justify the cost of the drug or the effort for the patient and the family to undergo repeated intrathecal procedures and frequent multiple visits to the hospital.[23,24]

In our experience, <7.5% of the initial cohort left the program, 4.1% immediately after they started and only 3.3% in the follow-up. Using a patient-reported questionnaire to investigate if they felt there was a functional improvement that was clinically meaningful to them, 73.61% of the responders who completed the questionnaire felt that there had been an improvement that was mainly related to motor function. Interestingly, there was good concordance between the findings reported by the family and those measured by the functional scales. Further studies using more structured tools will help to investigate the impact of the new therapy on patients and caregivers' quality of life.

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## Author Contributions

M.Pa., G.C., V.A.S., S.M., C.Bru., M.C., M.S., E.A., M.Pe., A.D.A., B.B., G.B., P.T., F.S., R.D.S., M.Pi., O.G.,

E.B., G.V., F.D.T., and E.M. contributed to the conception and design of the study. M.Pa., G.C., V.A.S., S.M., C.Bru., M.C., M.S., E.A., M.Pe., A.D.A., P.T., F.S., R.D.S., S.L., E.B., G.V., and E.M. contributed to the acquisition and analysis of data. M.Pa., G.C., V.A.S., S.M., C.Bru., M.C., M.S., E.A., M.Pe., A.D.A., C.Bra., B.B., G.B., P.T., F.S., R.D.S., S.L., M.Pi., O.G., E.B., G.V., F.D.T., and E.M. contributed to drafting the text and preparing the figures.

## Potential Conflicts of Interest

M.S., M.Pa., B.B., G.B., P.T., F.S., S.L., M.Pe., O.G., and C.Bra have nothing to report. M.Pi., G.C., V.A.S., S.M., C.Bru., M.C., E.A., A.D.A., R.D.S., F.D.T., and G.V. have received funding from Biogen as speakers in sponsored symposia. A.D.A., C.Bru., E.M., E.B., and S.M. are principal investigator for ongoing Biogen/Ionis Pharmaceuticals clinical trials. E.B. and E.M. received funding as members of advisory boards and received grants for SMA studies from Biogen/Ionis Pharmaceuticals. Biogen/Ionis Pharmaceuticals owns patent rights to nusinersen, a drug used in this study.

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