**Supplementary Materials**

**Figure S1:** Main results Analysis Flowchart

Une image contenant texte, ligne, diagramme, Police

Description générée automatiquement

Figure S1: Presence or not of symptom/difficulty before treatment initiation helps to determine the patient’s trajectory depending on perception.

**Table S1:** Inclusion criteria: Study windows and Functional Scales

|  |  |  |  |
| --- | --- | --- | --- |
| **Study windows** | | | |
| Baseline | | A baseline visit is accepted when performed within three months before treatment initiation. If no assessment before treatment initiation exists, an assessment is accepted as baseline if performed within two weeks after treatment is initiated with the first Spinraza injection. | |
| Month 15 | | A Month 15 visit is accepted when performed either on the fifteenth month after treatment initiation, or if no assessment at Month 15 is possible, the next closest assessment thereafter. | |
| **The order of priority of scales according to age at treatment initiation and type of SMA** | | | |
| Age at treatment initiation | SMA type | | Scales in order of priority |
| From 3 – 24 months | Type I (‘non-sitter’) | | 1. CHOP-INTEND 2. HINE-2 |
| From 6 – 24 months | Type II (‘sitter’) | | 1. CHOP-INTEND 2. HINE-2 |
| From 18 – 24 months | Type III (‘walker’) | | 1. CHOP-INTEND 2. HINE-2 |
| From 24 months | Type I | | 1. CHOP-INTEND 2. HINE-2 3. HFMSE 4. MFM32/MFM20 5. RULM |
| From 24 months | Type II | | 1. HFMSE 2. MFM32/MFM20 3. RULM |
| From 24 months | Type III | | 1. HFMSE 2. MFM32/MFM20 3. RULM |
| From 36 months | Type III | | 1. HFMSE 2. 6MWT 3. MFM32/MFM20 4. RULM |

Table S1: List of validated functional scales: Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); Hammersmith Infant Neurological Examination – Section 2 (HINE-2); Hammersmith Functional Motor Scale Expanded (HFMSE); Motor Function Measure 32 and 20 (MFM32; MFM20; Revised Upper Limb Module (RULM); 6-minute walk test (6MWT).

All scales have been used in SMA-related clinical trials for disease-modifying therapies and are usually recommended in clinical follow-up of patients treated with Spinraza. CHOP-INTEND was considered and accepted for all non-sitter patients regardless of their age because it is still commonly used in clinical follow-up for older non-sitter patients. The 6MWT has been widely used to assess functional exercise capacity in ambulatory patients with SMA. However, to be consistent with the other categories, motor function scales like the HFMSE instead of the 6MWT for the ambulant patients were prioritized.

**Table S2:** Assignment to Responder groups

|  |  |  |  |
| --- | --- | --- | --- |
| Scales | Month 15: point change to be considered as Responder clinically significant (RCS) | Month 15: point change to be considered as Responder non-clinically significant | Month 15: point change to be considered as Non-responder (NR) |
| CHOP-intend | >= 4 points | < 4 points; > 0 points | 0 points/meters; loss of points/meters |
| HINE-2 | >= 2 points | < 2 points; > 0 points |
| HFMSE | >= 3 points | < 3 points; > 0 points |
| MFM32 | >= 3 points | < 3 points; > 0 points |
| RULM | >= 2 points | < 2 points; > 0 points |
| 6MWT | >= 30 meters | < 30 meters; > 0 meters |

Table S2: The scores thresholds considered as clinically significant improvement according to each functional scale based on literature and our classification.

**Table S3:** Questionnaire

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Question | Domain | Question | Domain | Question | Domain |
| 1 | General Impression | 9 | Ability to eat a whole meal | 17 | Nocturnal ventilation support |
| 2 | Tremor | 10 | Appetite | 18 | Diurnal ventilation support |
| 3 | Balance while sitting | 11 | Frequency of aspiration during the day | 19 | Coughing |
| 4 | Balance while standing/waking | 12 | Swallowing | 20 | Frequency of respiratory infections |
| 5 | Fatigability | 13 | Chewing | 21 | Frequency of hospitalizations due to respiratory infections |
| 6 | Functions that involve the muscles of hands and wrists (writing, typing, using a joystick, drawing, colouring, etc.) | 14 | Loudness of voice | 22 | Pain |
| 7 | Functions that involve the muscles of arms (eating alone, brushing teeth, combing hair, applying make-up, etc.) | 15 | Having a continuous conversation |
| 8 | Functions that involve the muscles of shoulders (washing the hair, reaching objects above the head, etc.) | 16 | Quality of sleep |

Table S3: Questionnaire: Each question refers to one specific aspect/domain of patient’s quality of life and is scored with the PGIC scoring system.

**Table S4:** Perception of patients for each question of the questionnaire across the responder groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Questions (n=22) | RCS  (n= 41) | RNCS  (n=18) | NR  (n= 40) | Raw p-value |
| Mean Rank | | |
| Change in quality of life | 46.9 | 54.9 | 46.9 | 0.57 |
| Change in tremor | 56.3 | 50.6 | 43.3 | 0.07 |
| Change in balance while sitting | 57.1 | 51.7 | 41.9 | **RCS > NR p adjusted=0.03** |
| Change in balance while standing/walking | 56.7 | 43.7 | 45.9 | 0.12 |
| Change in fatigue | 50.6 | 60.0 | 44.9 | 0.14 |
| Change in function involving hand and wrist muscles | 55.3 | 54.1 | 42.7 | 0.08 |
| Change in function involving arm muscles | 58.2 | 43.4 | 44.6 | 0.03, \*RCS>NR p adjusted =0.06 |
| Change in function involving shoulder muscles | 59.90 | 44.03 | 42.54 | **RCS>NR, p adjusted=0.006** |
| Change in ability to eat | 50.7 | 52.2 | 48.3 | 0.79 |
| Change in appetite | 50.5 | 55.8 | 46.9 | 0.39 |
| Change in aspiration | 55.6 | 50.8 | 43.9 | **RCS>NR, p adjusted=0.024** |
| Change in swallowing | 50.4 | 50.7 | 49.2 | 0.95 |
| Change in chewing | 51.6 | 52.4 | 47.3 | 0.58 |
| Change in loudness of voice | 52.3 | 55.3 | 45.2 | 0.19 |
| Change in capacity for continuous conversation | 51.5 | 58.7 | 44.5 | 0.06 |
| Change in quality of sleep | 57.0 | 50.6 | 42.5 | **RCS > NR, p adjusted=0.01** |
| Change in need for nocturnal ventilation | 51.8 | 52.5 | 47.0 | 0.26 |
| Change in diurnal ventilation | 49.7 | 56.6 | 47.3 | **RNCS > NR, p adjusted=0.03** |
| Change in cough | 50.8 | 51.8 | 48.4 | 0.86 |
| Change in frequency of respiratory infections | 47.8 | 51.7 | 51.5 | 0.76 |
| Change in the frequency of hospitalization due to respiratory infection | 48.1 | 54.8 | 49.9 | 0.53 |
| Change in recurrent disease-related pain | 53.1 | 47.9 | 47.8 | 0.55 |

Table S4: Perception of patients scored by using the Patient Global Impression of change (PGIC) presented in mean rank by using Kruskal Wallis test. Significant results had a Bonferroni correction for multiple comparisons and are in bold. Significances with adjusted p-value <0.05 are in bold. \*Adjusted p-value for change involving the arm muscles is not significant after Bonferroni correction.