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Nusinersen Treatment in Adults with Severe Spinal Muscular Atrophy:

A Real-Life Retrospective Observational Cohort Study

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ABSTRACT

Background and Objectives: Spinal muscular atrophy (SMA) is a progressive neurodegenerative disease due to homozygous loss-of-function of the survival motor neuron gene *SMN 1* with absence of the functional SMN protein. Nusinersen, a costly intrathecally administered drug approved in 2017 in Europe, induces alternative splicing of the *SMN2* gene, which then produces functional SMN protein, whose amount generally increases with the number of *SMN2* gene copies.

Methods: We retrospectively collected data from consecutive wheelchair-bound adults with SMA managed at a single center in 2018-2020. The following were collected at each injection, on days 1, 14, 28, 63, 183, and 303: 32-item Motor Function Measurement (MFM) total score and D2 and D3 subscores; the Canadian Occupational Performance Measure (COPM) performance and satisfaction scores; and lung function tests. The patients were divided into two groups based on whether their MFM total score was $<$ or \geq the mean (15.6%). Adverse events were recorded.

Results: We identified 18 patients who received 4 to 8 nusinersen injections. No significant improvements occurred over time in any of the MFM scores or lung function test results, which did not differ between groups. The COPM performance score improved significantly from day 0 to day 303 in the high-MFM group and the COPM satisfaction score in the overall population from D0 to D183. Half the patients achieved the minimal clinically important difference for both COPM scores.

Discussion: The overall stability of conventional motor assessment in this population with advanced disabilities is encouraging to use more sensitive tools based on self-perception and autonomy in daily life activities, such as COPM. Our finding of a significant COPM performance score improvement from days 0 to 303 only in the patients with initial MFM-32 scores above the mean in the population suggests that the severity of the baseline disabilities may affect treatment efficacy.

Classification of evidence: level IV, retrospective observational cohort study

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by a homozygous deletion in the survival motor neuron (*SMN*) 1 gene located in the q region of chromosome 5, hence the commonly used name 5q-SMA. Degeneration of the anterior horn cells of the spinal cord results in skeletal muscle atrophy predominating in the proximal-limb and axial muscles including the respiratory muscles, although the diaphragm is relatively spared. Depending on the age of onset and acquisition of motor developmental milestones, SMA is classified into five subtypes, from 0 to 4.¹ In a natural-history study, motor function declined over time in all subtypes, albeit at varying rates, notably in adults.² In the forms with survival to adulthood, the motor weakness can progress to complete tetraplegia.

The *SMN1* gene is a telomeric gene that encodes the fully functional SMN protein. There is also a centromeric *SMN2* gene that differs from the *SMN1* gene only 7 nucleotides difference

between the SMN genes and affects exon 7 splicing, leading to exclusion from about about 85% of transcripts during splicing of the pre-mRNA. The resulting truncated protein is not functional and is rapidly degraded. The number of copies of the *SMN2* gene varies across individuals and, in general but not always, a higher copy number is associated with less severe symptoms in patients with SMA.

Nusinersen is one of the recently approved targeted treatments for SMA. This antisense oligonucleotide targets the intronic splicing silencer N1 located immediately downstream of exon 7 and responsible for inhibiting the inclusion of exon 7 into the mRNA transcript. Nusinersen thus induces alternative *SMN2*-gene splicing with inclusion of exon 7 in the final mRNA transcript.¹ It must be administered by intrathecal injection. Nusinersen was the first drug to be approved for the treatment of SMA, based on the results of randomized controlled trials in infants and children.^{3,4} No randomized placebo-controlled trials in adults have been published. In France, nusinersen has been available for adults with types 1 and 2 SMA since September 2018; type 3 was added in August 2019, although for each patient the treatment must be approved by a national committee of experts. Intrathecal administration of nusinersen is more challenging in adults with SMA than in children, as many adults have undergone spinal fusion to treat scoliosis related to axial muscle weakness, and guidance using an imaging modality is often needed. Furthermore, the efficacy data from pediatric studies cannot be readily extrapolated to adults, whose disease is generally more advanced. Although several single-center reported real-life experience of the treatment ⁵⁻⁹, additional data on

adult's population benefice are needed, notably to help determine the continuation and disruption criteria.

The objective of this single-center retrospective observational cohort study was to report real-life clinical experience of Nusinersen treatment in a cohort of adults severely affected with SMA type I to III, followed in Raymond-Poincaré university hospital, France.

METHODS

Study design and patients

We conducted a single-center retrospective observational study in consecutive adults with 5q-SMA who received nusinersen treatment in the neurology and intensive care departments of the Raymond-Poincaré University hospital (Garches, France) between September 2018 and August 2020. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Paris-Saclay ethics committee (#CER-Paris-Saclay-2021-006). French law does not require patient informed consent for retrospective studies of anonymized data.

Inclusion criteria were 5q-SMA confirmed by genetic testing; feasibility of intrathecal injections according to an evaluation by a neuroradiologist; patient request for nusinersen therapy; and, for patients with type 3 disease, approval by a committee of experts, in compliance with French regulations.

Nusinersen therapy

Nusinersen was injected intrathecally in a dosage of 12 mg per injection on days 1, 14, 28, and 63 then every 4 months, as recommended by the manufacturer. The injections were performed by neuroradiologists under fluoroscopic or computed tomography guidance, by lumbar puncture with local anesthesia. Each patient was admitted for 24 hours for each injection to allow monitoring. Patients remained supine for 2 hours after each injection and were monitored closely for the first 3 hours to ensure the prompt detection of any early adverse effects.

Data collection

The study data were abstracted from the medical files of each patient.

Global motor function was evaluated using the 32-item Motor Function Measurement (MFM-32), a generic scale designed to assess motor function in children and adults with neuromuscular disease. The total score can range from 0% to 100%. The items are divided into three domains, and a sub-score can be determined for each: D1 score assesses standing position, ambulation, and transfers; D2 score axial and proximal limb motor function; and D3 score distal limb motor function.

Self-perception of performance in the domains of self-care, productivity, and leisure was evaluated using the Canadian Occupational Performance Measure (COPM). This instrument is administered during a 30-minute semi-structured interview. The first step involves identifying daily activities that are meaningful to the patient, who then rates these activities on a 10-point scale according to their importance. The patient then selects the five activities that are most important but also most difficult to carry out. For each of these activities, the patient evaluates performance and satisfaction with performance on two 10-point scales.

Two occupational therapists have been trained for COPM and MFM assessment and had realized all assessment for our patients.

Respiratory function tests included vital capacity measurements in the seated and supine positions, maximum inspiratory and expiratory pressures, and sniff nasal inspiratory pressure.

Statistics

The statistical analysis was carried out using Statistica 10 software (TIBCO Software, Palo Alto, CA). Continuous variables were described as median [interquartile range] and categorical variables as n (%). For the analysis of functional evaluations, lung function evaluations and COPM, we have separated the study patients into two groups based on whether their total MFM-32 score was $<$ or \geq the mean in the overall population, reported as high or low-score MFM subgroup.

Several repeated measures ANOVA were used to evaluate the outcome measures (MFM D2 score, MFM D3 score and MFM total score, Grip and pinch strength, the COPM Performance score and the Satisfaction score, Vital Capacity seated, External Pressure, Internal Pressure and SNIP) as the first factor, injection day (1, 63, 183 [5th injection], or 303 [6th injection]) as the second factor MFM group (MFM low score and MFM high score).

We also determined the number (%) of patients who achieved the minimal clinically important difference (MCID) in the COPM scores, i.e., the smallest change that individual

patients considered important. *P* values smaller than 0.05 were taken to indicate significant differences.

All the data used for the analysis are available upon reasonable request to the corresponding author.

RESULTS

Patients

We reported 18 patients who received nusinersen at our center during the study period, 6 females and 12 males, aged from 21 to 39 years at baseline. One of them is type I, 5 type Ibis, 11 type II and 3 type III. Most of them had 3 copies of gene SMN2 (14/18, 77.8%). None of them are ambulatory. Fourteen patients (77.8%) required non-invasive ventilation, 4 (22.2%) required a tracheostomy. Median body mass index (BMI) of the patients was 17.6 ± 5.1 and the median weight before treatment was $43.0 \text{ kg} \pm 17.2$. Two patients (11.1%) required a gastrostomy for nutritive support. Seventeen patients (94.4%) had surgical arthrodesis, at median age 13.0 ± 4.3 (11-16) in average. Baseline median Walton's score was 9, corresponding sitting position impossible without assistance, drink or feed without assistance impossible, and baseline median Boston's score was 8, corresponding to moving permanently with a rolling chair use by themselves in average. Distribution of the number of nusinersen injections was as follows: 4, n=1; 5, n=3; 6, n=8; 7, n=4; and 8, n=2. Table 1 reports their main characteristics.

Outcome measures

*MF*M-32

The mean total MF*M*-32 score was 15.6%. Of the 18 patients, 10 had scores below 15.6% and 8 had scores equal to or greater than 15.6%. Figure 1 shows the changes over time in the total MF*M*-32 total score and D2 and D3 sub-scores. Only 2 patients type 3 SMA had a high score MF*M*.

Table 2 reports the MF*M*-32 total score and D2 and D3 sub-scores, and distal strength quantification with grip and pinch over time. None of these three variables changed significantly over time in the overall population ($P=0.37$, $P=0.70$, and $P=0.53$, respectively),

and none differed significantly between the low-MFM-32 and high-MFM-32 sub-groups ($P=0.98$, $P=0.94$, and $P=0.86$, respectively).

Canadian Occupational Performance Measure (COPM)

Table 3 reports the values of the COPM performance and satisfaction scores. For the COPM performance score, half the patients exceeded the MCID threshold, 5/10 low-MFM patients, and 4/8 high-MFM patients. The score improved significantly from day 0 to day 303 in the high-MFM group ($P=0.01$).

The COPM satisfaction score improved significantly between day 0 and day 183 in the overall population ($P=0.02$). Half the patients in the overall population and half in each sub-group exceeded the MCID threshold.

Respiratory function testing

Table 4 reports the respiratory function test results according to MFM-32 scores $<$ or \geq the mean (15.6%) in the total group. No significant differences were found for any of the tested parameters (vital capacity, maximal inspiratory and expiratory pressures, and sniff nasal inspiratory pressure).

DISCUSSION

The objective of this article was to report real-life clinical experience in a cohort of adults severely affected during the first year of nusinersen therapy in adults with 5q-SMA. We found no significant changes in the objective outcome measures, including the MFM-32 score, and distal strength. This absence of significant change was noted in the overall study population and in the two subgroups separated based on whether the MFM-32 total score was below or at least equal to the mean value in the overall population. However, regarding perceived satisfaction assessed using the COPM scores, half the patients in the overall population and in MFM high score subgroup achieved the MCID. In the high-MFM sub-group, perceived performance improved significantly between days 0 and 303, while in the overall population perceived satisfaction improved significantly from day 0 to day 183.

Several prospective studies have documented motor function gains with nusinersen therapy. Unlike other studies in patients with less severe disease, particularly prospective studies,⁵⁻⁹ we found no motor-function gains between baseline and 14 months. A slight improvement at

6 months was not maintained, and motor function decreased from 14 months onward, returning to the baseline score. Hagenhacker et al, Maggi et al., and Yeo et al. suggested a cumulative effect with an increasing percentage over time of patients reporting clinically significant improvements in Hammersmith Functional Motor Scale Expanded (HFMSSE) scores, irrespective of age. ^{6,8,9} However, Bram de Wel et al. recently reported a slight decrease in dominant-hand grip strength at 14 months, compared to 6 months, with similar decreases in the 6-minute walk test result and forced vital capacity. ⁷ Walter and co-workers had previously made a similar observation, without explaining it. Instead, Osmanovic et al. found that adults with SMA perceived a wearing-off of the treatment effects after nearly half of 51 investigated nusinersen administrations, chiefly within the last month before the next administration¹⁰.

Our results are less spectacular than those reported by others are. In particular, a German multicenter study demonstrated greater than 10-point HFMSSE-score improvements in 3% of patients. All these patients had type 3 disease, with or without loss of ambulation ⁸. Also, an Italian study showed an HFMSSE-score increase of up to 3 points in patients with SMA type 3 ⁹. Contrary to the studies by Hagenacker et al and Walter et al., which showed a motor-function deterioration in 8% of patients and a 1- to 2-point loss in the Revised Upper Limb Module (RULM) score in 2 of 17 patients, respectively, our study did not detect any deterioration in motor function ^{5,8}. In the prospective part of the study by de Wel et al., only the Medical Research Council (MRC) sum score improved significantly in the non-ambulatory sub-group, i.e., in the patients with more severe disease, at months 6 and 14⁷. We explain these discrepancies by the heterogeneity of patient populations, with a spectrum ranging from near quadriplegia to preserved ambulation. In addition, motor function was assessed using a wide variety of tools such as the HFMSSE, RULM, MFM, or only the MRC sum score. Finally, individual performance shows obvious fluctuations, and studies of test reproducibility have demonstrated inter-individual variability.

Interestingly, in our cohort, patients in the high-MFM subgroup noticed greater performance improvements with nusinersen therapy, suggesting that patients with less severe disease may benefit the most. This may partly explain some of the discrepancies across studies regarding the efficacy of nusinersen, notably when pediatric and adult patients were pooled.

Even small changes in motor performance may be important to the patients, as they may increase self-sufficiency and satisfaction. This point prompted us to determine the COPM performance and satisfaction scores, which reflect patients' perceptions of how they are

faring. The COPM performance score improved significantly in the high-MFM group from baseline to day 303 and the COPM satisfaction score in the overall population and both subgroups from baseline to day 183. The tools used in previous studies to assess patient-reported outcomes vary widely, from the Peds QL Multidimensional Fatigue Scale (despite the study being in adults) ⁶ to the Short Form-36 generic quality of life questionnaire.⁷ Several studies did not rely on standardized tools, asking open-ended questions instead. ^{9,11,12} In a prospective longitudinal single-center study in 24 adults, expectations regarding the effects of Nusinersen therapy were high, notably regarding disease stabilization, and 75% of patients reported better strength, endurance and self-sufficiency, although the changes in objective motor scores were only slight. ¹² Thus, absence of further deterioration in motor function is appreciated by patients, and Nusinersen therapy may improve perceived quality of life to a degree greater than expected based on objective measures of motor function.

The overall safety of the treatment has been confirmed in all the studies regardless of their design with identical adverse effects to what we have observed, namely post procedure headache (35 %), back pain (22 %) and nausea (11%). None of patient would to stop the treatment because of adverse event. ⁸

The main limitations of our study are the retrospective design and small sample size. A major strength is the homogeneity of the population regarding the degree of disability. We are aware of the interpretation bias that a not-randomized, unblinded study can cause, but it is very difficult to organize a double-blind randomized study once the authorities already gave the marketing authorization, in particular when it was the only curative treatment available. Given the high cost and invasiveness of Nusinersen treatment, further studies in adults are needed, notably in patients with severe disabilities, to assess potential long-term benefits and to identify criteria for treatment initiation and discontinuation. This is a pilot study but it would be interesting to pool the data of treated patients of all neuromuscular reference centers in France, for a national or international multicenter project. It could confirm the usefulness of occupational tools and extend to evaluate the effectiveness of the treatment.

To conclude, the overall stability of conventional motor assessment in adult with severe disabilities due to 5q-SMA given nusinersen therapy during a year is encouraging to use more sensitive tools based on self-perception and autonomy in daily life activities, such as COPM. Our finding of a significant COPM performance score improvement from days 0 to 303 only in the patients with initial MFM-32 scores above the mean in the population suggests that the severity of the baseline disabilities may affect treatment efficacy.

Disclosures

- Claire LEFEUVRE, Marion SARLON, David ORLIKOWSKI, Noémie PETIT, Hélène PRIGENT, Bernard CLAIR and Djillali ANNANE report no disclosures.
- Marion BRISSET received sponsoring from Biogen for participation to scientific conferences.
- Tristan THIRY and Robert-Yves CARLIER received fees for teaching curses about SMA.
- Pascal LAFORET and Samuel POUPLIN received once honorarium from Biogen for board participation on assessment of the upper limb impairment of the person with SMA.
- This study is not sponsored.
- All the data used for the analysis are available upon reasonable request to the corresponding author.
- The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Paris-Saclay ethics committee (#CER-Paris-Saclay-2021-006).

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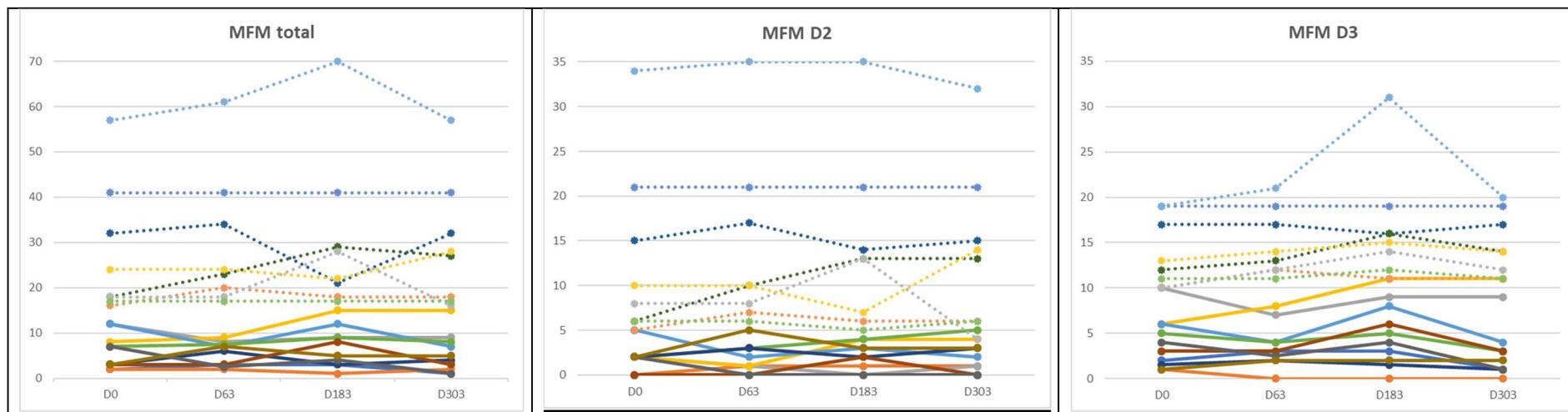
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Table 1: Characteristics of the study patients

| | |
|-----------------------------------------------|-----------------------|
| Number of patients | 18 |
| Females/Males | 6/12 |
| Baseline age, years, mean±SD (range) | 28.0 ± 5.9 (21-39) |
| SMA type, n (%) | |
| 1 | 1 (5.6) |
| 1bis | 5 (27.8) |
| 2 | 11 (61.1) |
| 3 | 3 (16.7) |
| SMN2 copy number, n (%) | |
| 2 copies | 3 (16.7%) |
| 3 copies | 14 (77.8%) |
| 4 copies | 2 (11.1%) |
| Respiratory assistance, n (%) | |
| Noninvasive ventilation | 14 (77.8%) |
| Tracheostomy | 4 (22.2%) |
| Nutritional data | |
| Baseline BMI, mean±SD (range) | 17.6 ± 5.1 (9.9–29.4) |
| Baseline body weight, kg, mean±SD (range) | 43.0 ± 17.2 (24–85) |
| Gastrostomy, n (%) | 2 (11.1%) |
| Spinal fusion | |
| Yes | 17 (94.4%) |
| Age at spinal fusion, years, mean±SD (range) | 13.0 ± 4.3 (11–16) |
| Baseline self-sufficiency | |
| Walton's score, mean±SD (range) | 9 ± 0.9 (7–9) |
| Boston's score, mean±SD (range) | 8 ± 0.2 (8–9) |
| Nusinersen therapy | |
| Number of injections, mean±SD (range) | 6 ± 1.0 (4–8) |
| Guidance for the intrathecal injection, n (%) | |
| Fluoroscopy | 7 (38.9%) |
| Computed tomography | 12 (66.7%) |

BMI: body mass index

Figure 1: Changes in the MFM-32 score during nusinersen therapy



The dotted lines represent data from the 8 patients with MFM-32 scores equal to or above the mean in the total population and the solid lines data from the 10 patients with MFM-32 scores below the mean in the total population.

D: domain of the MFM-32 score

Domain 1 (standing position, ambulation, and transfers) is not shown. The domain-1 score was 4 before and 5 after nusinersen therapy in 1 patient and was 0 or 1 throughout the evaluation period in the other 17 patients.

Table 2: Median [interquartile range] MFM-32 scores, grip strength, and pinch strength in the overall population and in the sub-groups defined by Motor Function Measure (MFM)-32 scores < or ≥ the mean (15.6%) in the total

| | | MFM-32 | | | | | | Distal strength (g) | | | | | | | | |
|----------------------------------|---------------------------------|--------------|------------|---------------------|-------------|-----------------------|-------------|------------------------|------------|--------------------|------------|--------------------|------------|--------------------|------------|--------------------|
| | | D2 | | D3 | | Total | | Grip | | Pinch | | | | | | |
| | | Left | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left | Right | | | |
| All participants n=18 | Baseline | Day 0 | 3.5 | [2.0 ; 7.5] | 8.0 | [3,25 ; 11,75] | 12.0 | [4.0 ; 18.0] | 0.4 | [0.1 ; 0.8] | 0.3 | [0.1 ; 0.9] | 0.2 | [0.1 ; 0.4] | 0.2 | [0.1 ; 0.5] |
| | Difference in Total Score | Days 0–63 | 0.0 | [0.0 ; 1.0] | 0.25 | [-0.75 ; 1.0] | 0.25 | [0.0 ; 2.75] | 0.1 | [0.0 ; 0.1] | 0.0 | [0.0 ; 0.1] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| | | Days 0–183 | 0.5 | [-1.0 ; 1.75] | 1.0 | [0.0 ; 2.75] | 0.5 | [-0.75 ; 4.25] | 0.0 | [-0.1 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| | | Days 0–303 | 0.0 | [-0.75 ; 1.0] | 0.0 | [-1.0 ; 1.0] | 0.0 | [-0.75 ; 1.75] | 0.0 | [-0.0 ; 0.1] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| Low-MFM group n=10 | Baseline | Day 0 | 2.0 | [0.5 ; 2.0] | 3.5 | [1.62 ; 5.75] | 5.0 | [3.0 ; 7.75] | 0.1 | [0.0 ; 0.3] | 0.1 | [0.0 ; 0.1] | 0.1 | [0.0 ; 0.0] | 0.1 | [0.0 ; 0.1] |
| | Difference in Total Score | Days 0–63 | 0.0 | [-1.0 ; 1.0] | -0.5 | [-1.37 ; -0.5] | 0.25 | [-3.0 ; 1.0] | 0.0 | [0.0 ; 0.1] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| | | Days 0–183 | 0.5 | [-1.5 ; 1.75] | 0.5 | [0.0 ; 1.75] | 0.5 | [-0.75 ; 2.0] | 0.0 | [-0.1 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| | | Days 0–303 | 0.5 | [-0.75 ; 1.0] | -1.0 | [-1.75 ; -0.13] | 0.0 | [-2.5 ; 1.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| High-MFM group n=8 | Baseline | Day 0 | 9.0 | [6.0 ; 16.5] | 12.5 | [10.75 ; 17.5] | 21.0 | [17.75 ; 34.25] | 0.9 | [0.6 ; 1.5] | 0.9 | [0.5 ; 1.7] | 0.4 | [0.3 ; 0.5] | 0.1 | [0 ; 0.1] |
| | Difference in Total Score | Days 0–63 | 0.5 | [0.0 ; 2.0] | 1.0 | [0.0 ; 2.0] | 1.0 | [0.0 ; 4.0] | 0.1 | [0.1 ; 0.3] | 0.2 | [0.0 ; 0.3] | -0.1 | [-0.1 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| | | Days 0–183 | 0.5 | [-1.0 ; 2.0] | 1.5 | [0.75 ; 4.0] | 1.0 | [-0.5 ; 10.25] | 0.1 | [-0.1 ; 0.2] | 0.1 | [0.0 ; 0.2] | 0.0 | [-0.1 ; 0.0] | 0.0 | [0.0 ; 0.0] |
| | | Days 0–303 | 0.0 | [-0.5 ; 1.75] | 1.0 | [0.0 ; 1.25] | 0.0 | [0.0 ; 2.5] | 0.1 | [0.0 ; 0.1] | 0.1 | [0.0 ; 0.2] | 0.0 | [0.0 ; 0.0] | 0.0 | [0.0 ; 0.0] |

Table 3: Median [interquartile range] Canadian Occupational Performance Measure scores for performance and satisfaction in the overall population and in the sub-groups defined by Motor Function Measure (MFM)-32 scores < or ≥ the mean (15.6%) in the total population

| | | COPM | | | | | |
|----------------------------------|---------------------------|--------------|-------------|------------------------|--------------|----------------------|--|
| | | Performance | | | Satisfaction | | |
| All participants n=18 | Baseline | Day 0 | 19.0 | [13.75 ; 25.0] | 20.5 | [13.5 ; 24.5] | |
| | Difference in Total Score | Days 0–63 | 0.5 | [0.0 ; 3.75] | 0.0 | [-1.75 ; 5.75] | |
| | | Days 0–183 | 1.5 | [0.0 ; 3.75] | 2.0 | [2.0 ; 8.0]** | |
| | | Days 0–303 | 0.5 | [0.5 ; 3.0] | 2.0 | [2.0 ; 4.0] | |
| Low-MFM group n=10 | Baseline | Day 0 | 18.0 | [13.25 ; 22.75] | 20.5 | [13.5 ; 21.0] | |
| | Difference in Total Score | Days 0–63 | 1.0 | [0.0 ; 3.75] | 0.0 | [-1.5 ; 4.5] | |
| | | Days 0–183 | 1.5 | [0.0 ; 3.75] | 1.5 | [-0.75 ; 8.0] | |
| | | Days 0–303 | 0.5 | [0.0 ; 3.0] | 1.5 | [0.0 ; 4.0] | |
| High-MFM group n=8 | Baseline | Day 0 | 25.5 | [15.25 ; 27.5] | 21.0 | [14.5 ; 26.0] | |
| | Difference in Total Score | Days 0–63 | 0.5 | [-2.0 ; 3.5] | 2.5 | [-1.25 ; 5.5] | |
| | | Days 0–183 | 1.5 | [0.0 ; 4.0] | 2.5 | [0.75 ; 5.75] | |
| | | Days 0–303 | 1.0 | [-0.25 ; 5.0]* | 2.5 | [-0.25 ; 5.5] | |

* $P=0.01$

** $P=0.02$

Table 4: Lung function test results in the overall population and in the sub-groups defined by Motor Function Measure (MFM)-32 scores < or ≥ the mean (15.6%) in the total

| | Day of the evaluations | VC seated (L) | | MEP (cmH2O) | | MIP (cmH2O) | | SNIP (cmH2O) | |
|----------------------------------|------------------------|---------------|---------------|-------------|-----------------|-------------|-----------------|--------------|-----------------|
| All participants n=18 | Day 0 | 0.97 | [0.51 ; 1.44] | 23.00 | [15.0 ; 34.0] | 47.0 | [26.00;60.00] | 35.5 | [23.50;51.75] |
| | Day 63 | 1.01 | [0.50 ; 1.82] | 24.00 | [18.0 ; 32.0] | 55.0 | [30.0 ; 62.0] | 44.5 | [22.50;55.75] |
| | Day 183 | 0.96 | [0.51 ; 1.32] | 20.50 | [11.75 ; 30.0] | 46.0 | [22.0 ; 54.25] | 41.5 | [23.25;54.25] |
| | Day 303 | 0.94 | [0.54 ; 1.72] | 23.00 | [14.0 ; 29.0] | 44.0 | [24.0 ; 51.0] | 43.0 | [31.0 ; 59.0] |
| Low-MFM group n=10 | Day 0 | 0.75 | [0.50 ; 0.97] | 19.00 | [12.0 ; 29.0] | 26.0 | [23.0 ; 51.0] | 30.5 | [22.75 ; 39.0] |
| | Day 63 | 0.65 | [0.46 ; 1.05] | 23.00 | [13.0 ; 24.0] | 38.0 | [17.0 ; 59.0] | 34.5 | [22.5 ; 53.25] |
| | Day 183 | 0.58 | [0.50 ; 0.93] | 15.50 | [10.25 ; 20.75] | 35.0 | [18.25 ; 47.0] | 28.5 | [20.25 ; 50.25] |
| | Day 303 | 0.60 | [0.45 ; 0.96] | 15.50 | [12.75 ; 23.75] | 34.0 | [18.75 ; 45.75] | 45.0 | [26.75 ; 63.5] |
| High-MFM group n=8 | Day 0 | 1.68 | [1.04 ; 2.91] | 32.50 | [23.0 ; 40.0] | 62.0 | [45.5 ; 71.25] | 44.5 | [29.5 ; 63.0] |
| | Day 63 | 1.92 | [1.00 ; 2.53] | 31.50 | [26.25 ; 40.25] | 58.5 | [54.25 ; 70.0] | 47.5 | [35.5 ; 64.25] |
| | Day 183 | 1.56 | [0.99 ; 2.29] | 30.00 | [23.25 ; 32.25] | 56.5 | [37.0 ; 63.25] | 47.0 | [32.0 ; 52.25] |
| | Day 303 | 1.85 | [1.19 ; 2.07] | 29.00 | [28.0 ; 58.0] | 46.0 | [44.0 ; 75.0] | 43.0 | [33.0 ; 48.0] |

The data are median [interquartile range].

VC: vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; SNIP: sniff nasal inspiratory pressure