Validity and reliability of the Motor Function Measure (MFM32) in children with neuromuscular disorders (NMDs) and in individuals with Type 2 and non-ambulant Type 3 spinal muscular atrophy (SMA)

D Trudell, S Le Scouliier, H Staunton, K Gorni and C Vuillerot

1 Roche Products Ltd, Welwyn Garden City, UK; 2 Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland; 3 Department of Paediatric Physical Medicine and Rehabilitation, Hôpital Femme Mère Enfant, Centre Hospitalier Universitaire de Lyon, France.

Background
- SMA is a rare, genetic, progressive neuromuscular disease with a broad range of severity.
- The MFM32 is a valid, reliable motor function assessment for individuals with NMDs aged ≥2 years.
  - MFM32 is the primary endpoint in SUNFISH Part 2, a study investigating the efficacy and safety of risdiplam for patients with Type 2 or non-ambulatory Type 3 SMA, aged 2-25 years.
  - A 20-item version of the MFM was developed for use in children <7 years old to address limitations due to age-related development (i.e. changes in function unrelated to disease).
- The use of two different MFM versions in clinical trials is challenging as changes over time cannot be equated across populations of different ages due to differences in items attempted and their weight towards the total score.
- The objective of this poster was to evaluate the validity and reliability of the MFM32 in children with NMDs (including SMA) aged 2-5 years, and in individuals with Type 2 and non-ambulant Type 3 SMA aged ≥2 years (i.e. similar to SUNFISH clinical trial population, an ongoing Phase 3 study).

Methods
Analysis population
The analysis dataset was extracted from the MFM database provided by Hospices Civils de Lyon. Two populations were studied:
(1) patients with Type 2 and non-ambulatory Type 3 SMA, aged 2-25 years (n=81)
(2) patients with NMDs (including SMA) aged 2-5 years (n=84).

Outcome assessments
MFM32
- The MFM32 assessment includes 32 items across three domains:
  - D1 Standing, transfers and ambulation
  - D2 Axial and proximal motor function
  - D3 Dorsal motor function

Analyses
Sociodemographic descriptive statistics
- Descriptive statistics were calculated for the patients’ demographic characteristics at baseline.
Reliability
Internal consistency*
- Internal consistency of the MFM32 was assessed by calculating Cronbach’s alpha using the earliest complete MFM32 data for each patient.
  - *Cronbach alpha values ≥0.7 are considered acceptable.
Test-retest reliability*
- Test-retest reliability of the MFM32 total score was assessed by comparing scores at two time points in patients classified as stable.
- Stable patients were classified as:
  - patients with no change in CGI-S score between two time points for the 2-5 years’ population
  - patients with no change in CIG-S score and Vignos grade between two-time points for the 2-5 years’ population.
- ICC 2,1, a two-way, random, single-measure analysis of variance (subject by visit) was calculated to assess the test-retest reliability.
  - *ICCs ≥0.7 are considered acceptable.

Validity
Convergent validity
- Convergent validity of the MFM32 total score was assessed via Spearman rank correlations with Vignos grade (2-5 years’ only) and with CGI-S scores (both populations).
- A correlation of 0.4–0.6 is considered to be moderate, and >0.6 is considered to be strong.
- Correlations >0.6 were anticipated.

Known-groups validity
- Known-groups validity was assessed by comparing mean total MFM32 scores via analysis of covariance (controlling for age and gender) with groups defined by:
  - Vignos grade (mild and moderate versus severe and very severe) for both populations
  - Vignos grade (1-5 versus 6-25) for the 2-5 years’ population.
- Evidence of known-groups validity was demonstrated by p<0.05.

Meaningful within-patient change
- Distribution-based estimates of meaningful within-patient change were calculated (2-5 years’ population only) primarily using one SEM:
  - SDbaseline + 1.645 * SEM
  - The reliability value was provided by the two reliability estimates produced as part of the overall analysis.
  - 0.95(0.30), 0.95(0.30) and 0.95(0.30) at baseline.

Results
Patient demographics
- A total of 185 patients were included in the analysis, including 81 patients with SMA in the 2-5 years’ population and 17 with SMA in the 2-5 years’ population (Table 2).
- A total of 84 patients were included in the 2-5 years’ population, including 12 patients with Type 2 SMA, five with Type 3 SMA and 26 with DMD.

Table 2. Patient demographics characteristics at baseline in both populations

Validity
Convergent validity
- In the 2-5 years’ patient population:
  - MFM32 correlation with CGI-S: r=0.49.
  - In the 2-5 years’ patient population:
    - MFM32 correlation with CGI-S: r=0.49.
    - MFM32 correlation with Vignos grade: r=0.79.

Known-groups validity
- Known-groups validity was demonstrated by statistically significant discrimination of MFM32 scores between groups defined by CGI-S and Vignos grade (Figures 1 and 2).

Table 4. Meaningful within-patient change (2-5 years’ population)

Conclusions
- The findings of this study provided strong evidence that the MFM32 is a valid and reliable measure in both children with NMD aged ≥2 years and patients with Type 2 and non-ambulant Type 3 SMA aged ≥2 years.
- Excellent evidence of MFM32 reliability was demonstrated by high Cronbach’s alpha in analyses of internal consistency in both populations as well as excellent test-retest reliability in patients with no change in mobility (Vignos) in the 2-5 years’ population and no change in global disease severity (CGI-S) in both populations.
- Convergent validity was demonstrated by strong correlations of MFM32 with Vignos and moderate/strong correlations with CGI-S (r=0.48; 2-25 years).
- The MFM32 was able to discriminate between patients with mild/moderate versus severe/very severe global status (CGI-S), and between those who can versus those who cannot walk (Vignos).
- A meaningful within-patient change of 3–4 points (3.125–4.167 on the 0–100 total score) was estimated in the 2-25 years’ SMA Type 3/5 population.
- Given the progressive nature of SMA, a 3-4 point improvement should not be viewed as minimal (as arguably stabilization is meaningful) but as a higher threshold against which to assess treatment benefit.
- These results provide supportive evidence for the use of the MFM32 total score as the primary efficacy outcome measure in the SUNFISH study and for use in younger patients with SMA (aged 2-5 years).

Abbreviations
CGI-S: Clinical Global Impression of Severity; D: duchenne DMD: Duchenne muscular dystrophy; ICC: intraclass correlation coefficient; SD: standard deviation; Vignos: Motor Function Measures.

Acknowledgments
The authors would like to thank all of the patients who provided their data to the MFM database, and to the site staff for administering the assessments and collecting the data. The study was sponsored by Roche Products Ltd, Welwyn Garden City, UK. Statistical analysis was performed by Michelle Kim, PhD, of MediTech Media, UK, in accordance with the Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

References