Lessons Learned from MEPSEVII: Enzyme Replacement Therapy for MPS VII

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Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies

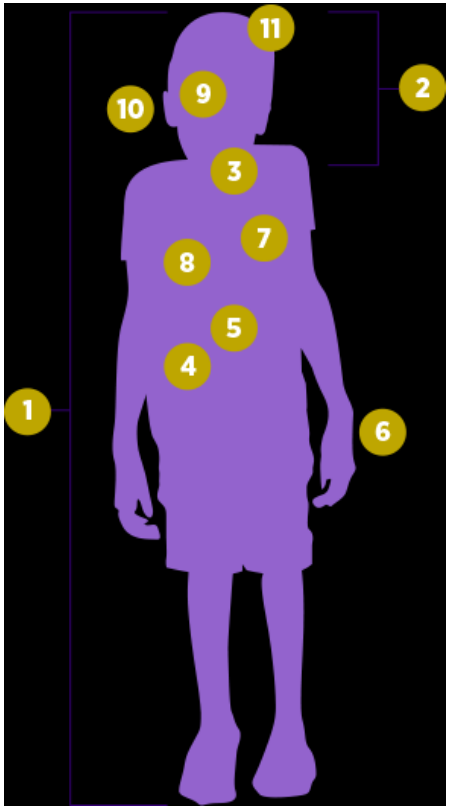
Sly Disease/MPS VII

- Cause:
  - autosomal recessive mutations in beta-glucuronidase gene (GUSB)
  - accumulation of glycosaminoglycans in connective tissue

- Incidence:
  - estimated 150 cases ever reported

Sly Disease/MPS VII

1. Short stature
2. “Coarse” facial features
3. Enlarged tonsils and adenoids
4. Hepatosplenomegaly
5. Umbilical or inguinal hernias
6. Pain due to bone and joint stiffness and carpel tunnel syndrome
7. Cardiomyopathy/valve dysfunction
8. Respiratory complications
9. Corneal clouding and cataracts in the eyes
10. Hearing loss and recurring ear infections
11. Developmental delay and progressive intellectual disability

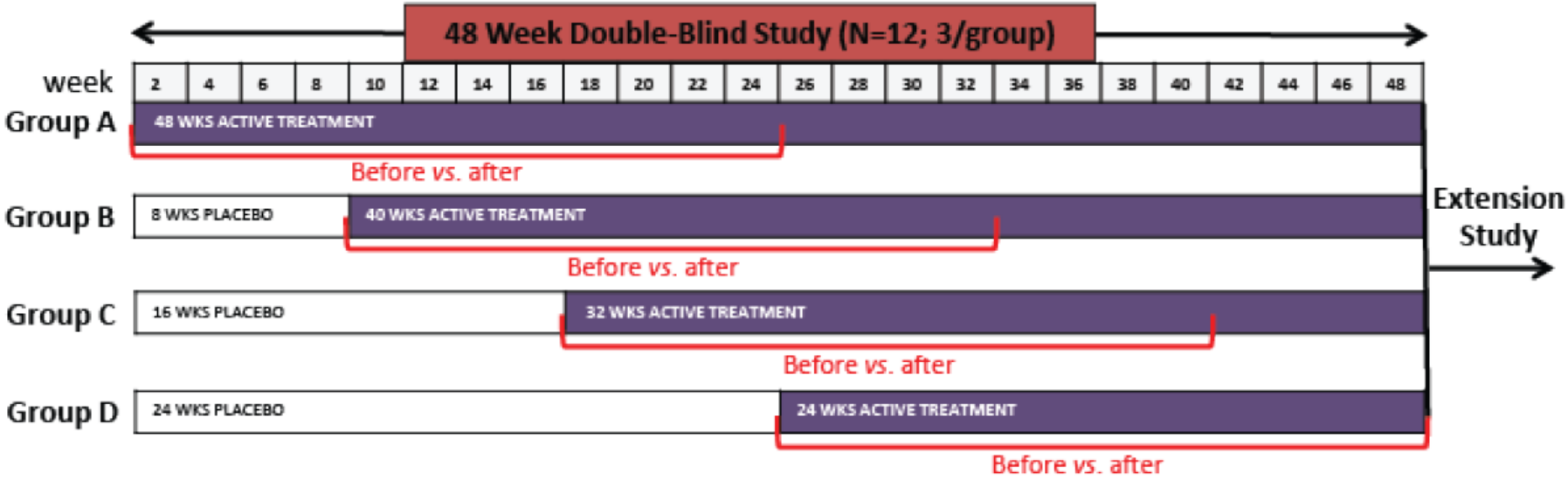


Adapted from http://mpsviiinfocus.com/what-is-mps-vii/
Montaño AM, Lock-Hock N, Steiner RD, et al. J Med Genet 2016;53:403–418.

Clinical Studies

Study	N	Study Design	Exposure Duration
Phase 3 (Study CL301)	12	Randomized, delayed start	24 weeks (initially) 48-112 weeks (subsequently)
Phase 1/2 (Study CL201)	3	Open label	~ 125 weeks
Expanded Access (EA)	2	Open label	~ 164 weeks

Pivotal Phase 3 Study CL301



MDRI Domain Components and Responder Definitions

Domain	Minimally Important Difference ("Responder Definition")
6-minute walk test (6MWT)	23 meter AND 10% change from baseline
Forced vital capacity (FVC)	5% absolute change or 10% relative change from baseline in FVC% predicted
Shoulder flexion	20-degree change of passive shoulder range of motion
Visual acuity	3-line improvement (corrected, both eyes) using Snellen chart
BOT-2[a] fine motor	Fine Motor Precision: change 0.72 Manual Dexterity: change of 1.47
BOT-2[a] gross motor	Balance: 0.57 Running Speed and agility: 0.59

[a]BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency

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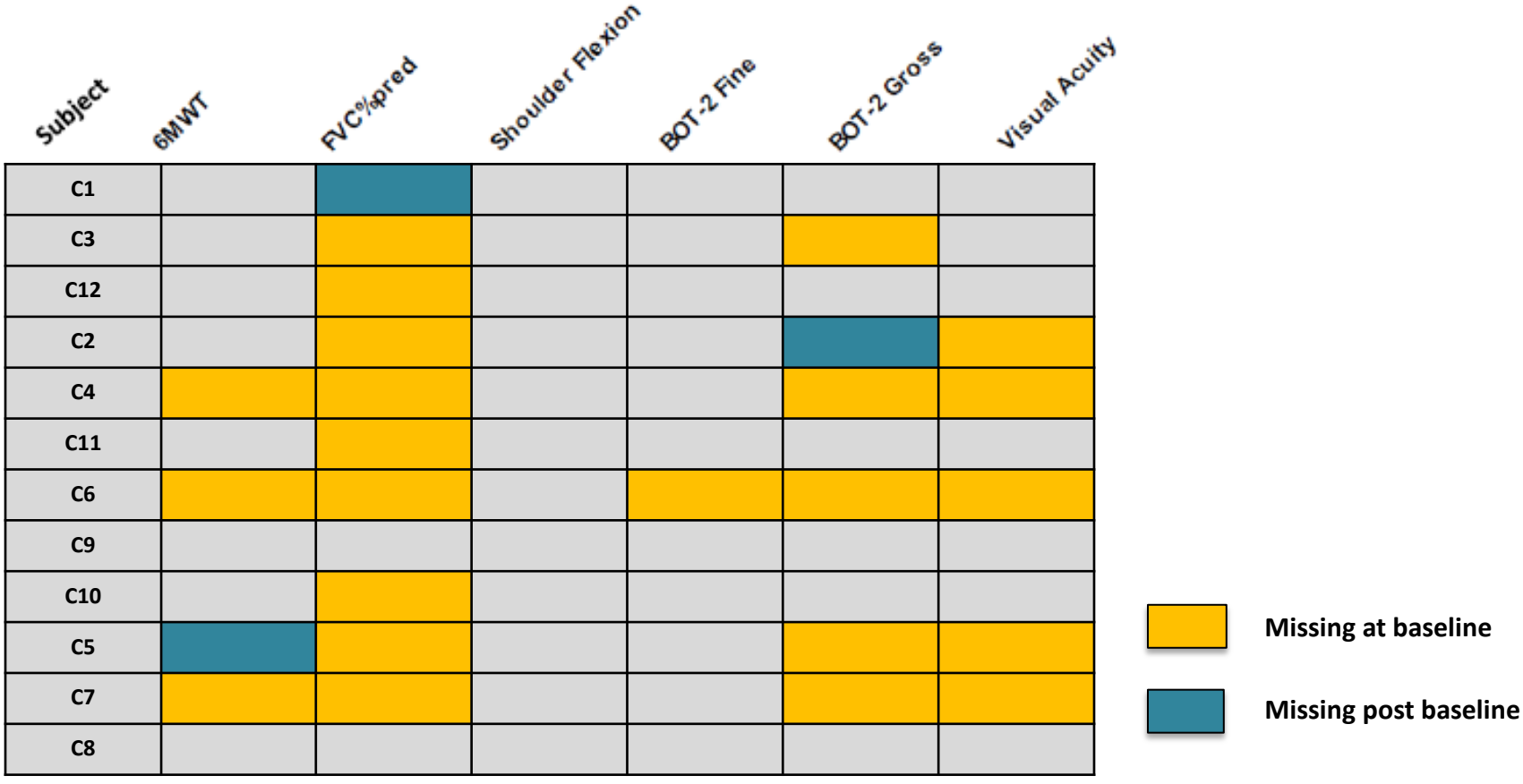

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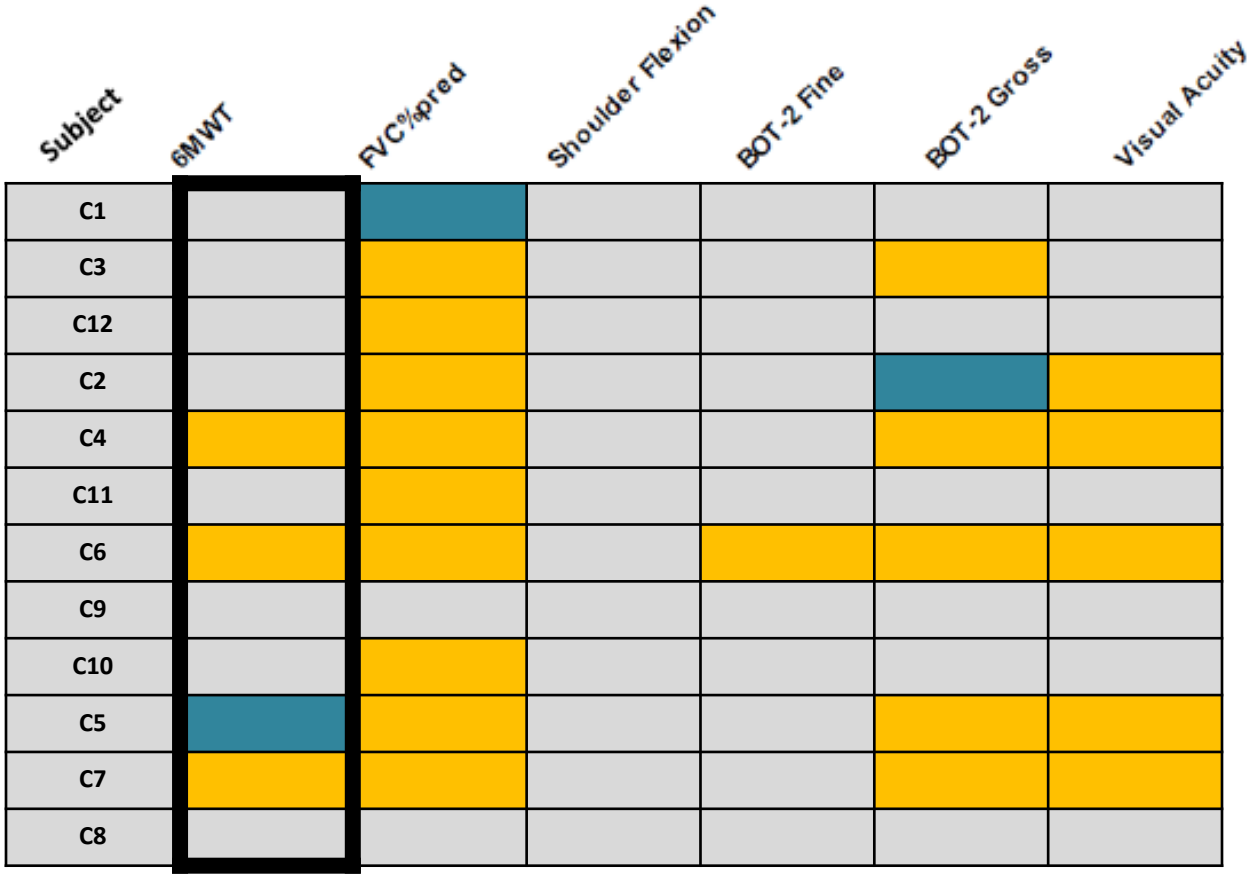

- **<u>6MWT:</u> Primary outcome measure**

Missing at baseline

Missing post baseline

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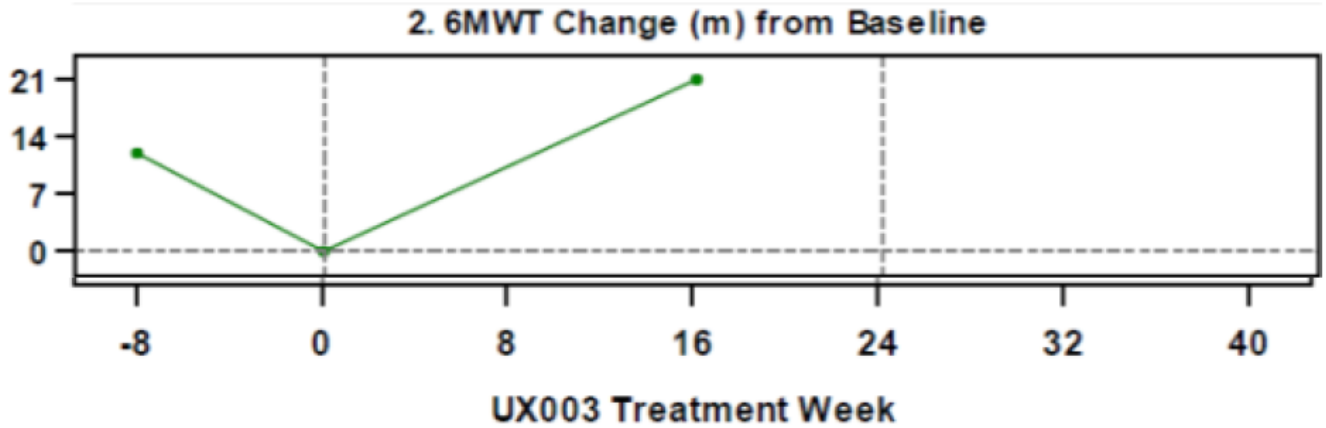

- *"Subject continues to do her own "way" stops and starts and never completes full laps.*

She does not cognitively understand testing ". The individual scoring the test did not

consider the test valid.

- *"Testing did not meet standard of acceptability and is not valid."*
- *"Not able to comprehend and follow test instructions."*

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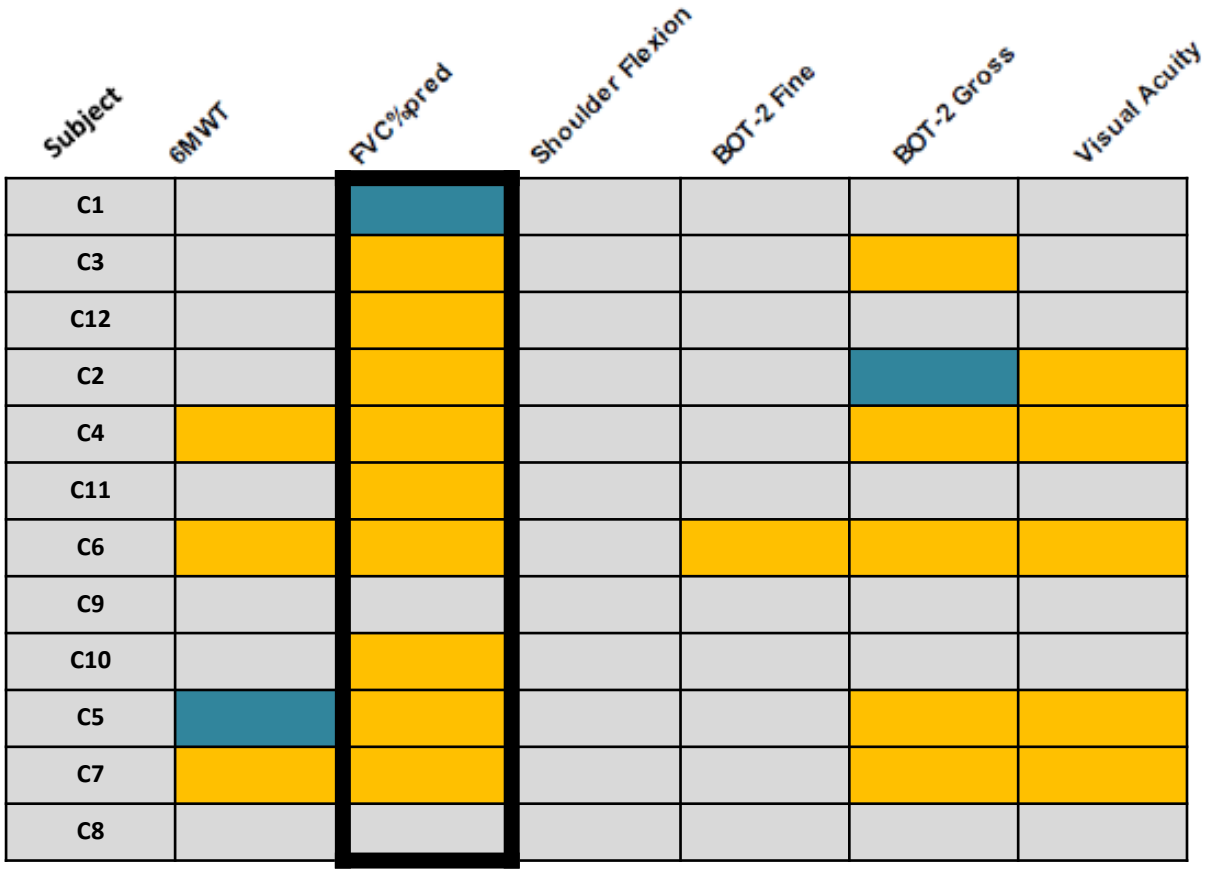

- **FVC % predicted: Patients were unable to complete testing as they did not understand the instructions**

Missing at baseline

Missing post baseline

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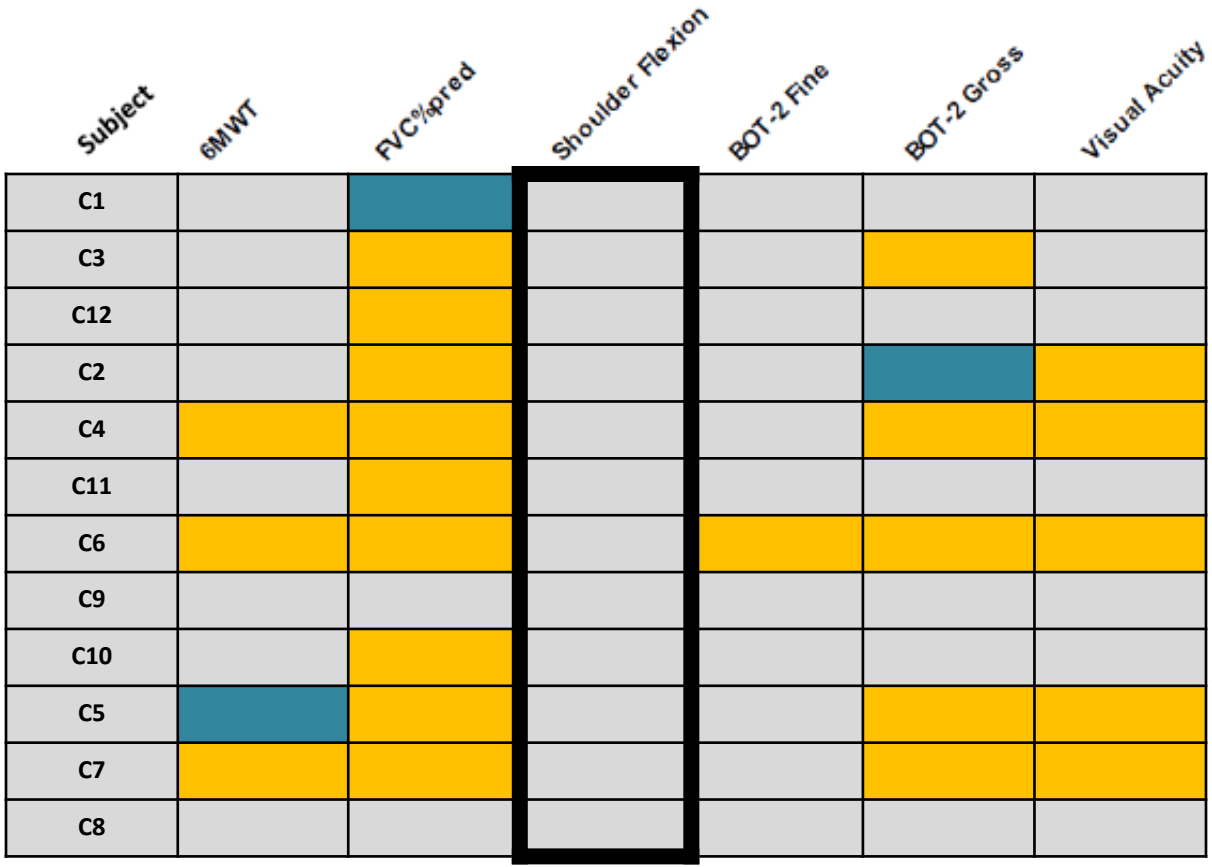

- **<u>Shoulder Flexion:</u> Patients demonstrated normal range of motion at baseline**

Missing at baseline

Missing post baseline

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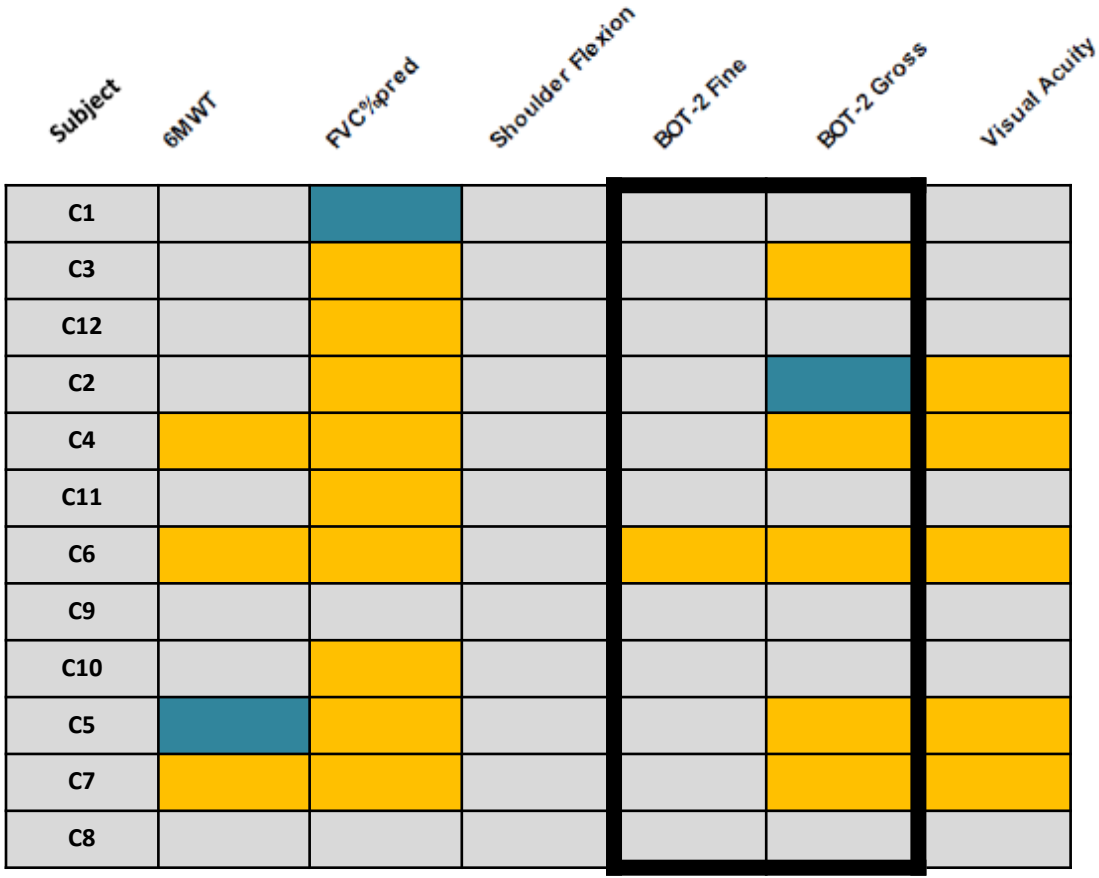
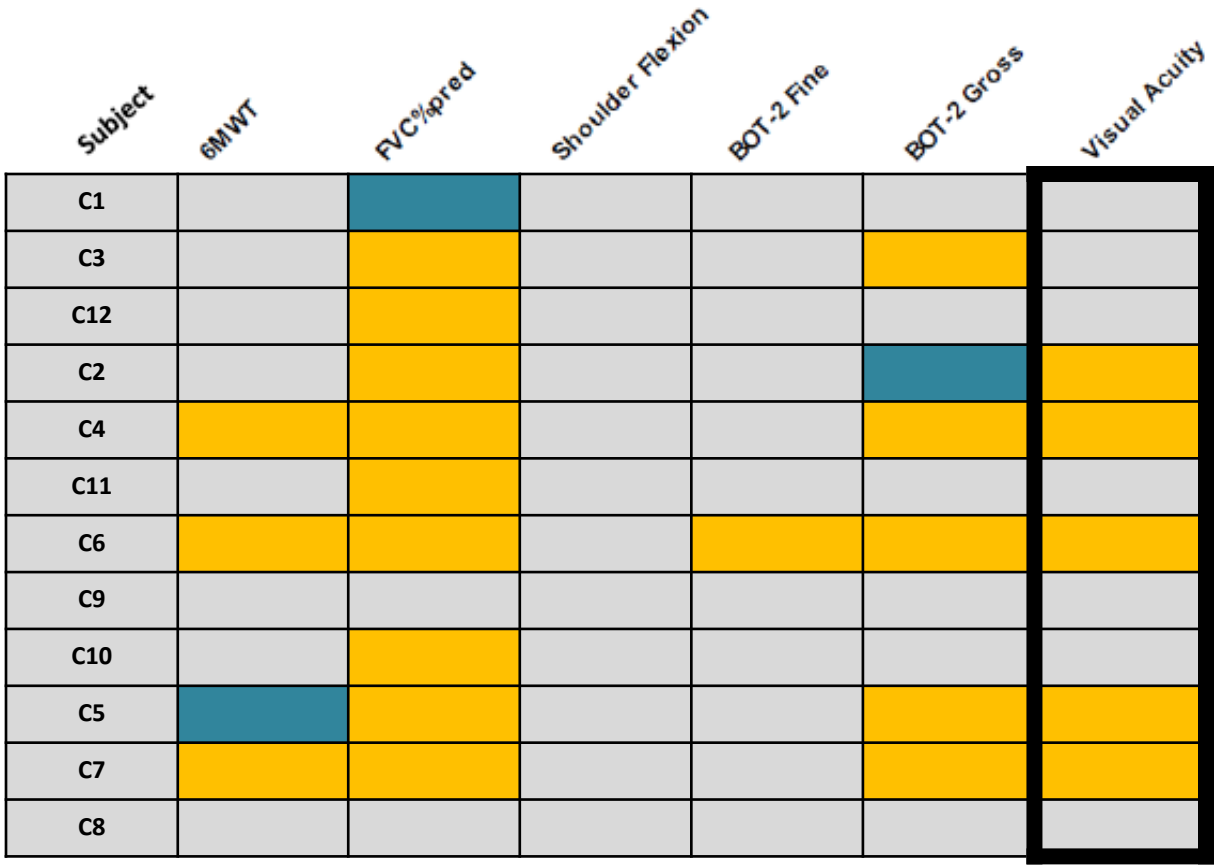


- **Bruininks-Oseretsky Test of Motor Proficiency (BOT-2):** Minimally important difference (MID) was based upon literature for group level, not individual level scores as would be appropriate
- **Fine Motor:**
  - Concern for the introduction of bias
  - Cognitive age equivalence of patients was near or below the test limit
- **Gross Motor:**
  - Most patients were unable to complete testing.
  - Scoring of "Balance" subtest was used as supportive evidence in patients who also improved 6MWT

Missing at baseline

Missing post baseline

MEPSEVII: Missing Data

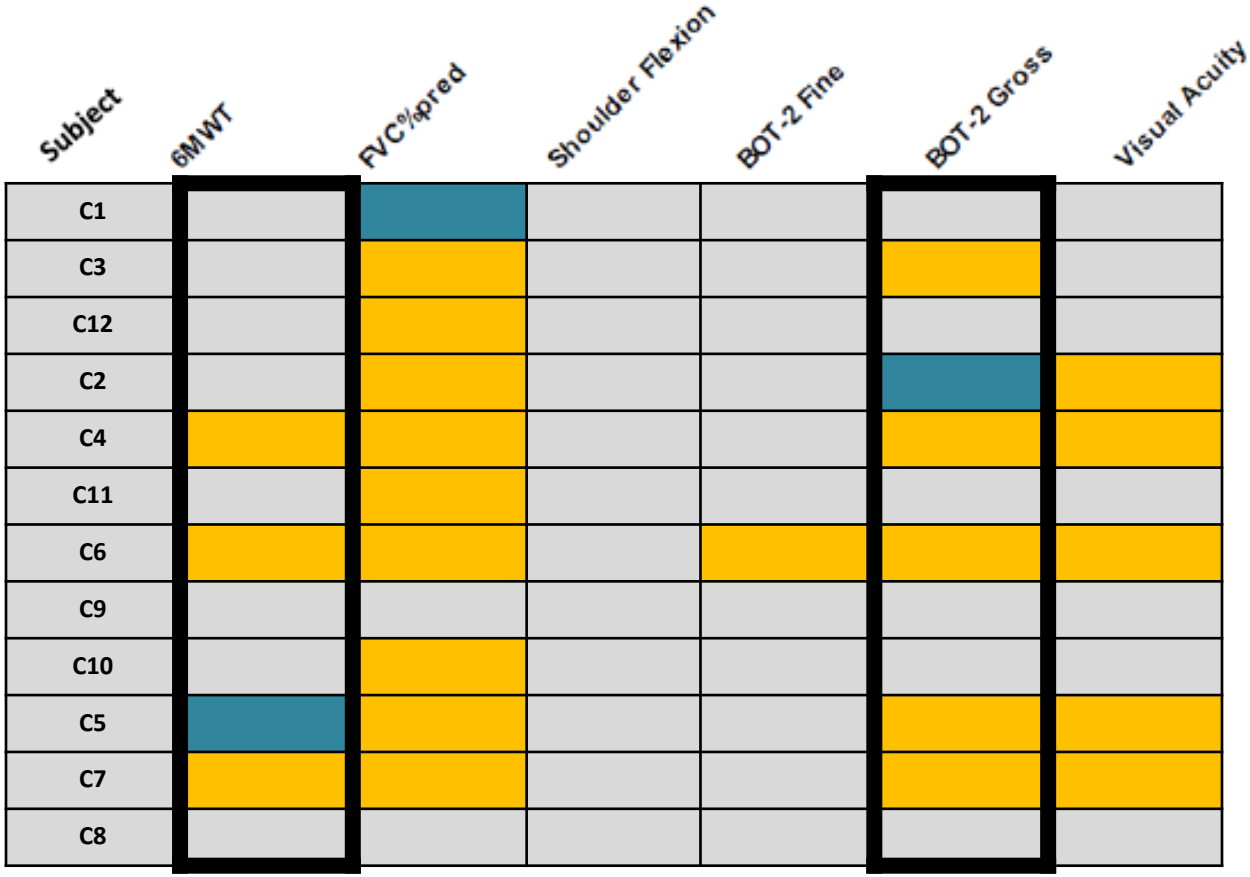


- **Visual Acuity:**
  - **Unable to comply with instructions**
  - **Protocol required evaluation with and without refraction (after evaluation for need)**
  - **Specific methodology (i.e. chart) used was vulnerable to false positive findings**

Missing at baseline

Missing post baseline

MEPSEVII: Study CL301



Data used for approval was limited to:

- **6MWT**
- **BOT-2 Gross Motor (supportive evidence)**

Missing at baseline

Missing post baseline

Basis for Approval

Study	Number of Patients	Reason
Phase 3 CL301	3 of 12	Clinically significant improvement in 6MWD from baseline that is supported by improvement in balance
Phase 1/2 CL201	1 of 3	Clinically significant improvement in % predictive FVC over time (compared to known natural history)
Expanded Access (EA)	1 of 2	Clinically significant reduction in the need for supportive ventilation over time (compared to known natural history)

- Demonstration of a change in pharmacodynamic biomarker, similar to other MPS based ERT
- Significant effort to facilitate patient recruitment
- Limited population of patients

MEPSEVII: Lessons Learned

- Not all MPS diagnoses have identical features
  - Study endpoints for any development program should be based upon knowledge of the specific disease population and the phenotypic variability within that population

- For diseases in which cognitive delay is a feature, an understanding of the spectrum of cognitive development and ability within patients is beneficial to inform endpoint selection and prevent missing data

- Trials should be of sufficient duration to allow for demonstration of impact on clinically meaningful endpoints

Future Considerations

- Baseline cognitive evaluations should be completed in all patients diagnosed with a disease that impacts neurocognition. This testing is informative for:
  - Disease pathology
  - Disease variability
  - Interpretation of selected evaluations

- Improvement in the development of functional tests that are not effort dependent can aide drug development in rare disease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MPS Diagnoses

MPS	Other Name	FDA Approved Treatment
MPS I	Hurler Syndrome Scheie Syndrome Hurler-Scheie Syndrome	ERT
MPS II	Hunter Syndrome	ERT
MPS III	Sanfilippo Syndrome (Types A to D)	No
MPS IV	Morquio Syndrome (Types A and B)	ERT
MPS V	*(See MPS I) Formerly Scheie Syndrome*	*(see MPS I)*
MPS VI	Maroteaux-Lamy Syndrome	ERT
MPS VII	Sly Syndrome	ERT
MPS IX	Hyaluronidase deficiency	No

Sources: https://mpssociety.org
https://rarediseases.org/rare-diseases/mucopolysaccharidoses/