

# JOURNEY: A Multicenter, Longitudinal, Natural History Study of Limb-Girdle Muscular Dystrophy

Linda P. Lowes,<sup>1</sup> Roberto Vincent,<sup>2</sup> Herb Stevenson,<sup>2</sup> Wenhua Hu,<sup>2</sup> Giacomo Comi<sup>3,4</sup>

<sup>1</sup>Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, OH; <sup>2</sup>Sarepta Therapeutics, Inc., Cambridge, MA; <sup>3</sup>Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; <sup>4</sup>Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy



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## Objective

To describe the baseline characteristics and functional assessments of participants with limb-girdle muscular dystrophies (LGMDs; 2E/R4, 2D/R3, and 2C/R5) enrolled in JOURNEY

## Key Findings

Baseline assessments showed that physical and pulmonary functions generally decreased with increasing age in both ambulatory and non-ambulatory participants

## CONCLUSIONS

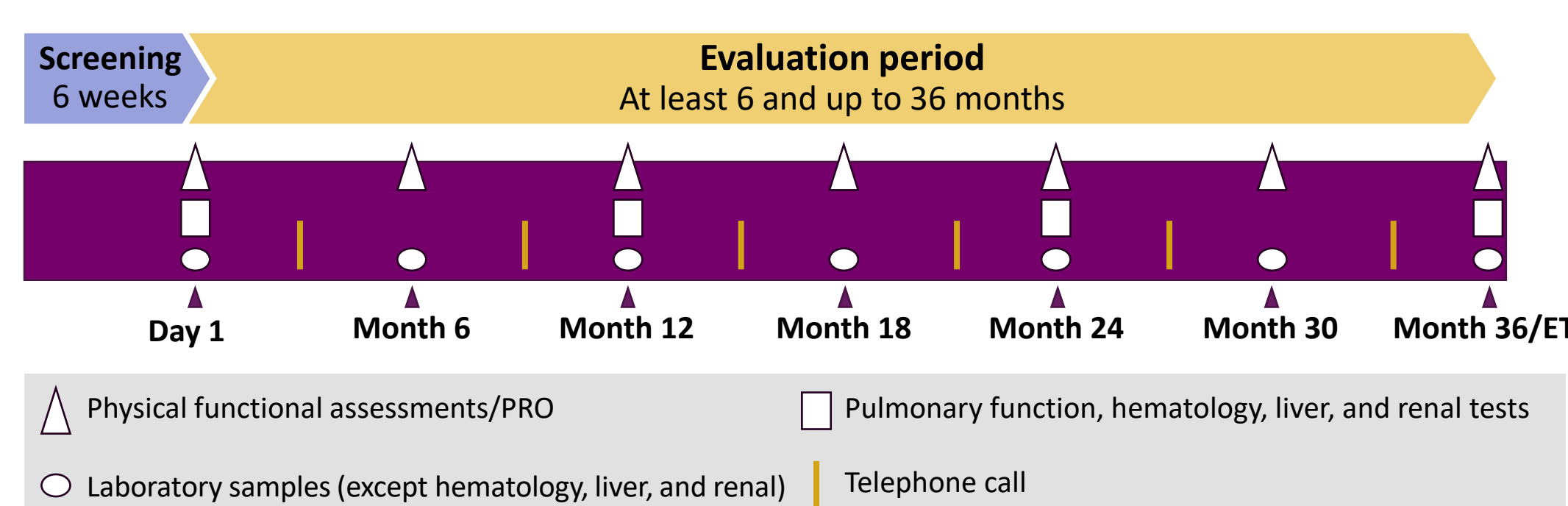
- JOURNEY is a natural history study of LGMD, adding to the overall understanding of clinical characteristics and disease progression of individuals with subtypes 2E/R4, 2D/R3, and 2C/R5
- Findings from interim analyses show that at baseline:
  - As expected, NSAD scores for older participants are substantially lower than those for younger participants across both ambulatory and non-ambulatory groups, suggestive of disease progression with age
  - Performance of PUL appears to be more heterogenous in non-ambulatory participants but declines with increasing age
  - Participants with LGMD2E/R4 appear to have an overall slightly better physical and pulmonary functional performance compared with the other 2 subtypes
  - There is a significant age overlap for participants who are still ambulatory vs participants who already lost ambulation
- Detailed analyses of additionally enrolled participants with LGMD are needed to verify whether these trends are consistent across a larger population

## BACKGROUND

- The LGMDs are a group of rare, genetically heterogeneous disorders involving progressive weakness and wasting of the shoulder and pelvic girdle musculature caused by defects in multiple genes encoding for proteins residing within the sarcolemma, cytosol, or the muscle cell nucleus<sup>1,2</sup>
- The sarcoglycanopathies, which represent ~15% of LGMDs in the US, are a group of autosomal recessive LGMDs caused by defects in the genes encoding 1 of the 4 cell membrane glycoproteins contributing to the sarcoglycan complex (SGCB, SGCA, SGCG, and SGCD)<sup>3</sup>
- As disease progresses, ambulatory function may deteriorate, with loss of ambulation (LOA) occurring in more than 60% of patients with LGMD<sup>4</sup>
- Current management for LGMD2E/R4, 2D/R3, or 2C/R5 subtypes is focused only on symptomatic and supportive treatments
- There is an urgent unmet need for restorative therapies
- JOURNEY (NCT04475926), a natural history study, was designed to characterize the clinical phenotype and disease course of patients with LGMD2E/R4, 2D/R3, and 2C/R5, including the natural variability among ambulatory and non-ambulatory populations
  - Here, we report the clinical characteristics and functional assessments of participants at baseline

## METHODS

Global, multicenter, longitudinal study of the natural history of participants with LGMD2E/R4, LGMD2D/R3, LGMD2C/R5 (NCT04475926)



### Planned enrollment

Cohort LGMD2E/R4 (N=30)	Cohort LGMD2D/R3 (N=30)	Cohort LGMD2C/R5 (N=30)
<ul style="list-style-type: none"> <li>4 to 7 years of age</li> <li>8 to 16 years of age</li> <li>≥17 years of age</li> </ul>	<ul style="list-style-type: none"> <li>4 to 7 years of age</li> <li>8 to 16 years of age</li> <li>≥17 years of age</li> </ul>	<ul style="list-style-type: none"> <li>4 to 7 years of age</li> <li>8 to 16 years of age</li> <li>≥17 years of age</li> </ul>

### Study population

- ≥4 years of age
- Clinical and genotypic confirmation of LGMD2E/R4, 2D/R3, or 2C/R5
- At least 10 ambulatory (defined in this study as ≥40% predicted on 100MWR timed test) subjects 4–16 years of age in each subtype
- At least 20 non-ambulatory (defined in this study as any subject who requires assistance to walk, uses a wheelchair part- or full-time, or is able to walk but falls below 40% predicted threshold on the 100-meter walk/run [100MWR] timed test) subjects ≥4 years of age in each subtype

### Primary endpoints

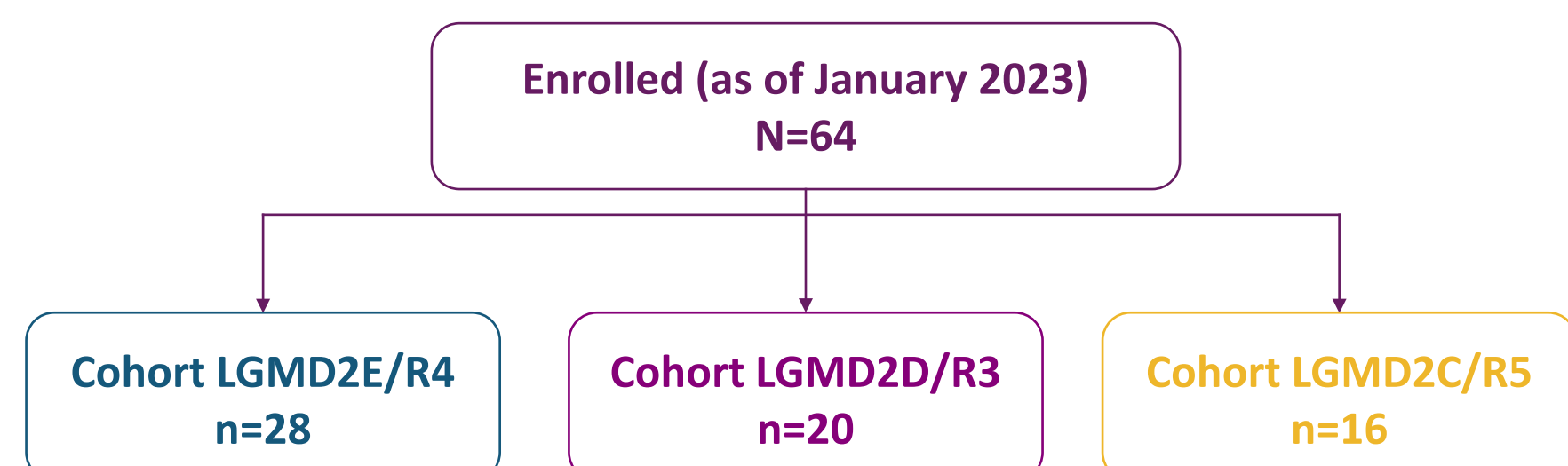
- Physical functional assessments
  - North Star Assessment for Limb Girdle-type Dystrophies (NSAD) score
  - Time to ascend 4 steps
  - Performance of upper limb (PUL)
  - Timed up and go (TUG)
  - 100MWR
  - Pulmonary function tests
  - Forced vital capacity
  - Forced expiratory volume

### Exploratory endpoints

- Electrocardiogram
- Echocardiogram
- Cardiac magnetic resonance imaging (MRI)
- Skeletal MRI
- Wearable device data
- Patient-reported outcomes

## RESULTS

### Enrollment



### Baseline Characteristics Stratified by LGMD Subtypes (as of January 2023)

Characteristic	LGMD2E/R4			LGMD2D/R3			LGMD2C/R5		
	Age 4–7 y (N=3)	Age 8–16 y (N=8)	Age ≥17 y (N=17)	Age 4–7 y (N=3)	Age 8–16 y (N=5)	Age ≥17 y (N=12)	Age 4–7 y (N=1)	Age 8–16 y (N=6)	Age ≥17 y (N=9)
<b>Age, years</b>									
Mean (SD)	5.0 (1.00)	11.5 (2.39)	31.1 (10.29)	5.3 (1.53)	11.2 (3.63)	44.3 (14.00)	6.0 (NE)	12.5 (3.02)	31.9 (6.53)
Median (min, max)	5.0 (4, 6)	10.5 (9, 16)	29.0 (18, 57)	5.0 (4, 7)	10.0 (8, 16)	43.0 (24, 70)	6.0 (6, 6)	12.0 (9, 16)	34.0 (21, 42)
<b>Gender, n (%)</b>									
Male	3 (100)	3 (37.5)	10 (58.8)	2 (66.7)	4 (80.0)	4 (33.3)	0	3 (50.0)	3 (33.3)
Female	0	5 (62.5)	7 (41.2)	1 (33.3)	1 (20.0)	8 (66.7)	1 (100)	3 (50.0)	6 (66.7)
<b>Ambulatory status, n (%)</b>									
Ambulatory	3 (100)	6 (75.0)	5 (29.4)	3 (100)	5 (100)	7 (58.3)	1 (100)	5 (83.3)	1 (11.1)
Non-ambulatory	0	2 (25.0)	12 (70.6)	0	0	5 (41.7)	0	1 (16.7)	8 (88.9)
<b>Creatine kinase levels, n</b>									
Mean (SD), U/L	2	8	17	2	4	11	1	6	8
	10909.0 (5094.0)	6293.0 (3311.40)	2272.0 (2476.70)	16505.0 (10311.03)	10307.3 (6345.50)	800.7 (604.71)	10851.0 (NE)	3612.2 (2619.20)	465.0 (265.93)
<b>Medical history, n (%)</b>									
Cardiac disorders	0	0	9 (52.9)	0	0	1 (8.3)	0	1 (16.7)	5 (55.6)

### Functional Assessments at Baseline: Ambulatory Participants

	LGMD2E/R4			LGMD2D/R3			LGMD2C/R5		
	Age 4–7 y (N=3)	Age 8–16 y (N=6)	Age ≥17 y (N=5)	Age 4–7 y (N=3)	Age 8–16 y (N=5)	Age ≥17 y (N=7)	Age 4–7 y (N=1)	Age 8–16 y (N=5)	Age ≥17 y (N=1)
<b>Physical functional assessments</b>									
<b>NSAD total score, n</b>	3	6	5	2	5	6	1	5	1
Mean (SD)	47.3 (3.06)	42.0 (15.56)	25.8 (11.82)	40.5 (14.85)	30.6 (10.85)	33.5 (11.08)	43.0 (NE)	25.6 (13.58)	10.0 (NE)
<b>Time to ascend 4 steps, n</b>	3	6	3	2	3	5	1	4	0
Mean (SD), sec	2.5 (1.07)	8.0 (11.21)	10.9 (6.42)	3.7 (2.12)	4.8 (2.04)	5.0 (2.77)	2.5 (NE)	8.4 (7.77)	
<b>PUL total score, n</b>	3	6	5	2	5	6	1	5	1
Mean (SD)	37.3 (1.53)	38.2 (4.88)	32.4 (7.57)	27.0 (5.66)	30.4 (5.94)	35.3 (5.92)	35.0 (NE)	30.2 (8.50)	23.0 (NE)
<b>TUG, n</b>	3	5	3	2	3	6	1	3	0
Mean (SD), sec	6.1 (1.54)	6.2 (1.78)	11.8 (7.36)	6.6 (3.47)	7.8 (3.56)	10.4 (3.19)	5.7 (NE)	7.3 (3.52)	
<b>Time of 100MWR, n</b>	3	6	5	2	4	6	1	4	0
Mean (SD), sec	30.7 (25.50)	87.6 (100.41)	150.5 (117.12)	66.8 (41.58)	58.9 (42.63)	89.2 (25.80)	59.0 (NE)	96.3 (49.58)	
<b>Pulmonary functional assessments<sup>b</sup></b>									
<b>FEV1%, n</b>	2	6	5	1	5	6	1	4	1
Mean (SD)	105.1 (47.93)	85.9 (8.71)	79.0 (11.00)	97.4 (NE)	86.6 (15.55)	76.3 (13.46)	102.7 (NE)	89.7 (12.05)	110.6 (NE)
<b>FVC%, n</b>	2	6	5	1	5	6	1	4	1
Mean (SD)	95.8 (45.60)	82.5 (11.46)	76.5 (6.07)	92.2 (NE)	91.4 (15.67)	76.2 (12.10)	96.7 (NE)	94.3 (18.87)	100 (NE)

<sup>a</sup>Recommended minimum age for the PUL=7. Improvement over time in 4–7-year-olds is due to maturation. <sup>b</sup>Many children under the age of 7 cannot perform the 10MWR test, which may explain lower values in the 4–7-year-old cohorts.

- Within ambulatory participants, baseline NSAD total scores, time to ascend 4 steps, and TUG were worse in older participants
- PUL total score was similar across all 3 cohorts in ambulatory participants but was lower in non-ambulatory participants
- In non-ambulatory participants, PUL total score was similar for participants in the LGMD2C/R5 cohort but decreased notably in the 8–16-year-old age range to the ≥17-year-old age range in the LGMD2E/R4 cohort

### Functional Assessments at Baseline: Non-Ambulatory Participant

	LGMD2E/R4			LGMD2D/R3			LGMD2C/R5		
	Age 4–7 y (N=0)	Age 8–16 y (N=2)	Age ≥17 y (N=12)	Age 4–7 y (N=0)	Age 8–16 y (N=0)	Age ≥17 y (N=5)	Age 4–7 y (N=0)	Age 8–16 y (N=1)	Age ≥17 y (N=8)
<b>Physical functional assessments</b>									
<b>NSAD total score, n</b>	-	2	11	-	-	5	-	1	7
Mean (SD)		17.5 (21.92)	3.8 (4.05)			0.8 (1.30)		4.0 (NE)	1.0 (0.82)
<b>Time to ascend 4 steps, n</b>	-	1	1	-	-	0	-	0	0
Mean (SD), sec		6.7 (NE)	16.5 (NE)						
<b>PUL total score, n</b>	-	2	12	-	-	5	-	1	8
Mean (SD)		27.0 (15.56)	15.4 (11.17)			14.2 (6.83)		16.0 (NE)	14.8 (4.10)
<b>TUG, n</b>	-	1	0	-	-	0	-	0	0
Mean (SD), sec		8.6 (NE)							
<b>Time of 100MWR, n</b>	-	1	0	-	-	0	-	0	0
Mean (SD), sec		69.0 (NE)							
<b>Pulmonary functional assessments</b>									
<b>FEV1%, n</b>	-	2	12	-	-	4	-	1	8
Mean (SD)		96.4 (7.87)	50.5 (21.40)			56.7 (34.87)		89.9 (NE)	45.1 (22.35)
<b>FVC%, n</b>	-	2	12	-	-	4	-	1	8
Mean (SD)		91.5 (2.28)	50.3 (20.21)			52.3 (33.56)		91.5 (NE)	42.8 (20.85)

## ABBREVIATIONS

100MWR=100-meter walk/run timed test; ET=early termination; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; LGMD=limb-girdle muscular dystrophy; NE=not estimated; NSAD=North Star Assessment for limb girdle-type dystrophies; PRO=patient-reported outcome; PUL=performance of upper limb; sec=seconds; TUG=timed up and go; y=years.

## REFERENCES

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