T355

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

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Background

- The limb-girdle muscular dystrophies (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[1,2]
- 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*)[3]
- As disease progresses, ambulatory function may deteriorate, with loss of ambulation (LOA) occurring in more than 60% of patients with LGMD[4]
- 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 nonambulatory populations
  - Here, we report the clinical characteristics and functional assessments of participants at baseline

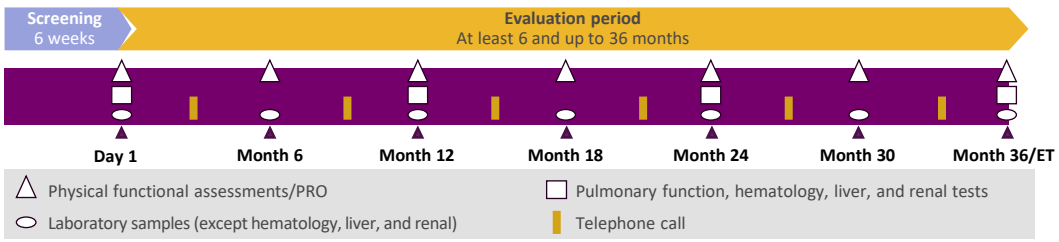
Objective

To describe the baseline characteristics and functional assessments of participants with LGMDs 2E/R4, 2D/R3, and 2C/R5) enrolled in JOURNEY

Methods

JOURNEY is a global, multicenter, longitudinal study of the natural history of participants with LGMD2E/R4, LGMD2D/R3, LGMD2C/R5 (NCT04475926) (**F1**)

F1 *JOURNEY Study Design*



Planned enrollment

Cohort LGMD2E/R4 (N=30)
- 4 to 7 years of age
- 8 to 16 years of age
- ≥17 years of age

Cohort LGMD2D/R3 (N=30)
- 4 to 7 years of age
- 8 to 16 years of age
- ≥17 years of age

Cohort LGMD2C/R5 (N=30)
- 4 to 7 years of age
- 8 to 16 years of age
- ≥17 years of age

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 threshold on the 100-meter walk/run [100MWR] timed test) subjects 4–16 years of age in each subtype
- At least 20 nonambulatory (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 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

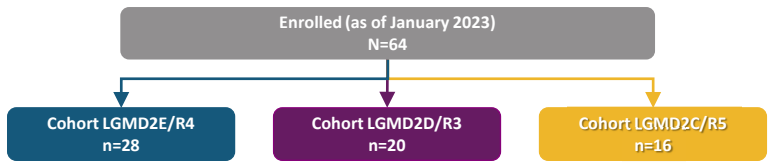
Exploratory endpoints

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

Results

- 64 participants were enrolled in JOURNEY (**F2**)
- LGMD2D/R3 participants were typically older and had a greater age range, and a higher percentage were ambulatory compared with other subtypes (**T1**)
- As expected in a degenerative disease, there was a higher percentage of ambulatory participants in younger age groups
- Cardiac disorders at baseline were observed in participants >17 years of age in all LGMD subtype cohorts
  - Beta-blocking medications were used by participants >17 years of age in all LGMD subtype cohorts
  - The most prevalent use was in the LGMD2E/R4 participants with 53% of participants >17 years of age reporting use
- Within ambulatory participants, baseline NSAD total scores, time to ascend 4 steps, and TUG were worse in older participants (**T2**)
- PUL total score was similar across all 3 cohorts in ambulatory participants but was lower in nonambulatory participants
- In nonambulatory 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

F2 *Enrollment*



T1 *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)
Age, years									
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)
Gender, n (%)									
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)
Ambulatory status, n (%)									
Ambulatory	3 (100)	6 (75.0)	5 (29.4)	3 (100)	5 (100)	7 (58.3)	1 (100)	5 (83.3)	1 (11.1)
Nonambulatory	0	2 (25.0)	12 (70.6)	0	0	5 (41.7)	0	1 (16.7)	8 (88.9)
Creatine kinase levels, n	2	8	17	2	4	11	1	6	8
Mean (SD), U/L	10,909.0 (5094.0)	6293.0 (3311.40)	2272.0 (2476.70)	16,505.0 (10,311.03)	10,307.3 (6345.50)	800.7 (604.71)	10,851.0 (NE)	3612.2 (2619.20)	465.0 (265.93)
Medical history, n (%)									
Cardiac disorders	0	0	9 (52.9)	0	0	1 (8.3)	0	1 (16.7)	5 (55.6)

T2 *Functional Assessments at Baseline: Ambulatory Participants and Nonambulatory Participants*

	LGMD2E/R4			LGMD2D/R3			LGMD2C/R5		
	Age 4–7 y	Age 8–16 y	Age ≥17 y	Age 4–7 y	Age 8–16 y	Age ≥17 y	Age 4–7 y	Age 8–16 y	Age ≥17 y
Ambulatory participants, n	**3**	**6**	**5**	**3**	**5**	**7**	**1**	**5**	**1**
Physical functional assessments									
NSAD total score, n	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)
Time to ascend 4 steps, n	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)	
PUL total score,[a] n	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)
TUG, n	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)	
Time of 100MWR,[b] n	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)	
Pulmonary functional assessments[b]									
FEV1%, n	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)
FVC%, n	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)
Nonambulatory participants, n	**0**	**2**	**12**	**0**	**0**	**5**	**0**	**1**	**8**
Physical functional assessments									
NSAD total score, n	-	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)
Time to ascend 4 steps, n	-	1	1	-	-	0	-	0	0
Mean (SD), sec		6.7 (NE)	16.5 (NE)						
PUL total score, n	-	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)
TUG, n	-	1	0	-	-	0	-	0	0
Mean (SD), sec		8.6 (NE)							
Time of 100MWR, n	-	1	0	-	-	0	-	0	0
Mean (SD), sec		69.0 (NE)							
Pulmonary functional assessments									
FEV1%, n	-	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)
FVC%, n	-	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)

[a]Recommended minimum age for the PUL=7. Improvement over time in 4–7-year-olds is due to maturation. [b]Many children under the age of 7 cannot perform the 100MWR test, which may explain lower values in the 4–7-year-old cohorts.

Key Findings

Baseline assessments showed that physical and pulmonary functions generally decreased with increasing age in both ambulatory and nonambulatory 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 nonambulatory groups, suggestive of disease progression with age
- Performance of PUL appears to be more heterogenous in nonambulatory 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

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.

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