94P

JOURNEY: A Natural History Study of Limb-Girdle Muscular Dystrophies R3-R5: Baseline Characteristics of Study Cohort

Linda P. Lowes[1], Carlos Ortez Gonzalez[2], Kristl G. Claeys[3], Chamindra G. Laverty[4], Andrea Gangfuss[5], Crystal M. Proud[6], Jordi Diaz Manera[7], Meredith K. James[7], Lindsay N. Alfano[1], Herb Stevenson[8], Lixi Yu[8], Giacomo Comi[9,10]

[1]Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA; [2]Neuromuscular Unit, Hospital Sant Joan de Deu, Barcelona, Spain; [3]Department of Neurology, University Hospitals Leuven and KU Leuven, Leuven, Belgium; [4]University of California San Diego, San Diego, CA, USA; [5]Department of Pediatric Neurology, Centre for Neuromuscular Disorders, Centre for Translational Neuro- and Behavioral Sciences, University Duisburg-Essen, Essen, Germany; [6]Children's Hospital of The King's Daughter, Norfolk, VA, USA; [7]The John Walton Muscular Dystrophy Research Center, Newcastle University. Newcastle Upon Tyne Hospitals NHS, Newcastle Upon Tyne, UK; [8]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [9]Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [10]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy

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]
- Progressive muscle degeneration in sarcoglycanopathies leads to loss of ambulation, respiratory difficulties, and often premature death[4]
- Current management for LGMD2E/R4, 2D/R3, and 2C/R5 subtypes is focused only on symptom relief and supportive treatments
  - There is an urgent unmet need for treatments that address the root cause of the disease
- Data on the clinical characteristics and natural history of LGMD are limited
  - JOURNEY (NCT04475926) is a natural history study designed to characterize the clinical phenotype and disease course of patients with LGMD, including the natural variability among ambulatory and nonambulatory populations

Objective

To describe baseline clinical characteristics and functional assessments of patients with LGMD2E/R4, 2D/R3, and 2C/R5 enrolled in JOURNEY (NCT04475926)

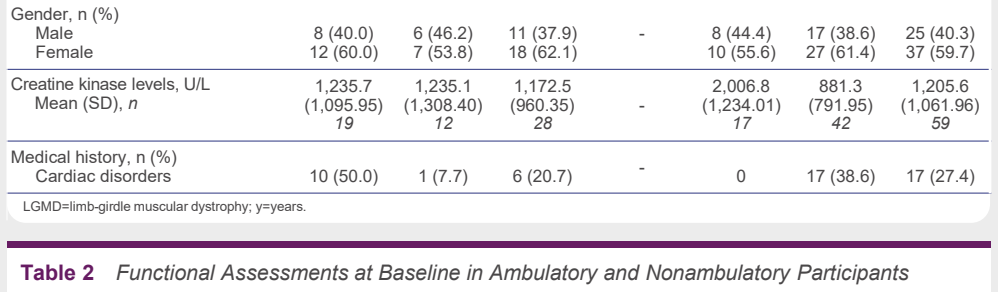
Methods

- JOURNEY is a global, multicenter, prospective, longitudinal study of the natural history of participants with LGMD2E/R4, 2D/R3, 2C/R5, and 2A/R1 (NCT04475926) (**Figure 1**)
  - This analysis only includes data from patients with sarcoglycanopathy subtypes (2E/R4, 2D/R3, and 2C/R5); data in patients with LGMD2A/R1 are not shown

Study population

- ≥4 years of age
- Clinical and genotypic confirmation of LGMD2E/R4, 2D/R3, 2C/R5
- Ambulatory (defined in this study as any subject with <30 seconds on the 10-meter walk/run [10MWR] test) or
- Nonambulatory (defined in this study as any subject with a 10MWR ≥30 seconds or unable to perform in the absence of a confounding illness or injury)

Figure 1 *JOURNEY Study Design*



Primary endpoints

Physical functional assessments
- North Star Assessment for Limb Girdle-type muscular dystrophies (NSAD)
- 4-stair climb (4SC)
- Ankle range of motion
- Performance of upper limb (PUL)
- Up and go
- 100-meter walk/run

Pulmonary function tests
- Forced vital capacity (FVC)
- Forced expiratory volume in 1 second (FEV1)
- Peak expiratory flow rate
- Maximal inspiratory pressure
- Maximal expiratory pressure

Exploratory endpoints

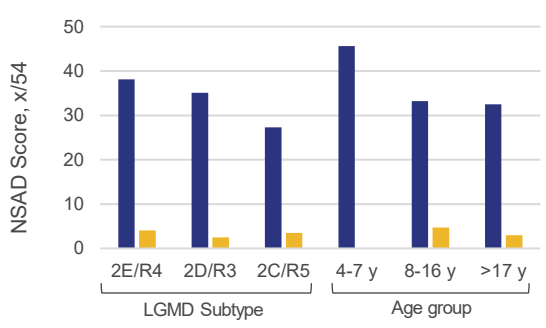
- Electrocardiogram (ECG)
- Echocardiogram
- Cardiac magnetic resonance imaging (MRI)
- Skeletal MRI
- Wearable device data
- Patient-/observer-reported outcomes

Results

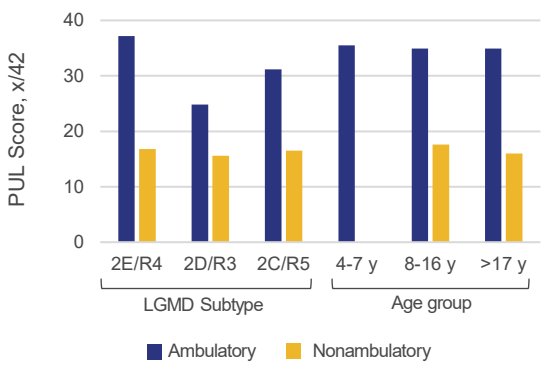
- 137 participants are enrolled in JOURNEY as of February 2024 (75 ambulatory and 62 nonambulatory), with a higher proportion of females (**Table 1**)
- As expected in a degenerative disease, there is a higher percentage of ambulatory participants in younger age groups
- Creatine kinase levels are significantly increased in all subgroups, and are ≥3 to 4 times higher in ambulatory than nonambulatory participants
- Cardiac disorders at baseline are most prevalent in nonambulatory participants ≥17 years of age
- 73 ambulatory and 59 nonambulatory participants have baseline ECG data available
  - 3/59 (5.1%) nonambulatory participants have clinically significant ECG abnormalities
  - 19/73 (26.0%) ambulatory and 32/59 (54.2%) nonambulatory participants have clinically insignificant ECG abnormalities at baseline
- 15–20% of all participants use steroid treatment
- Physical function assessments show worse results in older patients (**Figure 2, Table 2**)
  - NSAD, up and go, and 100-meter walk/run assessments progressively decline over the 3 age groups
  - In ambulatory participants, 4-stair climb velocity decreases in older participants while PUL scores remain unchanged
  - PUL scores decline in the nonambulatory population
- Pulmonary function assessments generally show worse outcomes in older nonambulatory participants

Figure 2 *Physical Functional Assessments at Baseline in Ambulatory and Nonambulatory Participants*

A *NSAD Scores by Subtype and Age Group*



B *PUL Scores by Subtype and Age Group*



LGMD=limb-girdle muscular dystrophy; NSAD=North Star Assessment for Limb Girdle-Type Muscular Dystrophies; PUL=performance of upper limb; y=year(s).

Table 1 *Baseline Characteristics Stratified by LGMD Subtype (as of February 2024)*

	LGMD 2E/R4 (n=45)	LGMD 2D/R3 (n=49)	LGMD 2C/R5 (n=43)	Age 4–7 y (n=10)	Age 8–16 y (n=59)	Age ≥17 y (n=68)	Total (N=137)
Ambulatory participants, n	**25**	**36**	**14**	**10**	**41**	**24**	**75**
Age, years Mean (SD)	15.7 (8.96)	23.2 (17.86)	10.9 (2.98)	5.8 (1.23)	11.8 (2.42)	34.9 (14.51)	18.4 (14.24)
Gender, n (%) Male Female	14 (56.0) 11 (44.0)	14 (38.9) 22 (61.1)	5 (35.7) 9 (64.3)	6 (60.0) 4 (40.0)	17 (41.5) 24 (58.5)	10 (41.7) 14 (58.3)	33 (44.0) 42 (56.0)
Creatine kinase levels, U/L Mean (SD), *n*	5,831.0 (4,260.33) *23*	5,244.3 (5,988.47) *34*	5,715.4 (4,561.40) *14*	13,561.1 (5,496.36) *9*	5,590.7 (4,255.29) *39*	2,275.8 (2,180.59) *23*	5,527.2 (5,152.77) *71*
Medical history, n (%) Cardiac disorders	2 (8.0)	0	1 (7.1)	0	1 (2.4)	2 (8.3)	3 (4.0)
Nonambulatory participants, n	**20**	**13**	**29**	**0**	**18**	**44**	**62**
Age, years Mean (SD)	29.7 (13.47)	29.7 (14.88)	22.2 (9.18)	-	13.7 (2.20)	31.3 (11.05)	26.2 (12.36)
Gender, n (%) Male Female	8 (40.0) 12 (60.0)	6 (46.2) 7 (53.8)	11 (37.9) 18 (62.1)	-	8 (44.4) 10 (55.6)	17 (38.6) 27 (61.4)	25 (40.3) 37 (59.7)
Creatine kinase levels, U/L Mean (SD), *n*	1,235.7 (1,095.95) *19*	1,235.1 (1,308.40) *12*	1,172.5 (960.35) *28*	-	2,006.8 (1,234.01) *17*	881.3 (791.95) *42*	1,205.6 (1,061.96) *59*
Medical history, n (%) Cardiac disorders	10 (50.0)	1 (7.7)	6 (20.7)	-	0	17 (38.6)	17 (27.4)

LGMD=limb-girdle muscular dystrophy; y=years.

Table 2 *Functional Assessments at Baseline in Ambulatory and Nonambulatory Participants*

	LGMD2E/R4 (n=45)	LGMD2D/R3 (n=49)	LGMD2C/R5 (n=43)	Age 4–7 y (n=10)	Age 8–16 y (n=59)	Age ≥17 y (n=68)
Ambulatory participants, n	**25**	**36**	**14**	**10**	**41**	**24**
Physical functional assessments[a]						
NSAD total score, x/54	38.1 (13.29) *25*	35.1 (12.66) *34*	27.3 (15.18) *14*	45.6 (7.93) *10*	33.2 (14.58) *40*	32.5 (12.31) *23*
4-stair climb Time, s Velocity, stairs/s	5.56 (6.72) 1.40 (0.80) *22*	4.37 (3.04) 1.27 (0.65) *29*	9.5 (13.08) 1.10 (0.81) *12*	2.73 (1.22) 1.70 (0.61) *10*	6.41 (9.26) 1.32 (0.77) *34*	6.2 (4.47) 0.99 (0.62) *19*
PUL total score, x/42	37.2 (5.63) *25*	24.8 (7.11) *35*	31.2 (8.18) *14*	35.5 (5.21) *10*	34.9 (7.22) *41*	34.9 (7.81) *23*
Up and go Time, s Velocity, ups/s	7.8 (4.32) 0.15 (0.06) *22*	8.8 (4.50) 0.14 (0.05) *29*	7.6 (3.48) 0.15 (0.06) *9*	6.3 (1.57) 0.17 (0.04) *10*	7.4 (3.41) 0.16 (0.06) *31*	10.7 (5.38) 0.11 (0.04) *19*
100-meter walk/run Time, s Velocity, m/s	82.8 (82.55) 2.01 (1.09) *23*	78.9 (53.96) 1.71 (0.94) *31*	120.9 (95.29) 1.25 (0.73) *12*	58.6 (34.88) 2.10 (0.78) *9*	85.6 (75.12) 1.82 (1.05) *34*	102.7 (81.00) 1.46 (0.92) *23*
Pulmonary functional assessments[a]						
FEV1%	89.9 (18.18) *21*	81.9 (19.54) *32*	93.1 (15.67) *13*	99.3 (22.62) *7*	88.4 (18.81) *37*	79.6 (15.03) *22*
FVC%	86.4 (18.26) *22*	87.0 (15.92) *32*	94.6 (14.46) *13*	92.7 (23.75) *8*	91.8 (15.32) *37*	80.9 (13.47) *22*
Nonambulatory participants, n	**20**	**13**	**29**	**0**	**18**	**44**
Physical functional assessments[a]						
NSAD total score, x/54	4.1 (3.82) *17*	2.5 (3.03) *12*	3.5 (3.28) *28*	-	4.7 (2.87) *16*	3.0 (3.49) *41*
PUL total score, x/42	16.8 (10.67) *19*	15.6 (6.39) *12*	16.5 (3.70) *29*	-	17.6 (3.41) *17*	16.0 (7.98) *43*
Pulmonary functional assessments[a]						
FEV1%	57.6 (23.31) *19*	63.6 (31.59) *10*	67.3 (26.12) *27*	-	83.5 (20.78) *16*	55.3 (23.74) *40*
FVC%	58.3 (23.07) *19*	60.5 (32.45) *10*	67.4 (24.58) *27*	-	85.2 (16.04) *16*	54.2 (23.19) *40*

[a]Values are mean (SD), *n*.
FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; LGMD=limb-girdle muscular dystrophy; m=meters; NSAD=North Star Assessment for Limb Girdle-type Dystrophies; PUL=performance of upper limb; s=second(s); y=years.

Key Finding

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:

- A higher proportion of participants in younger age groups are ambulatory; however, a substantial portion of participants ≥8 years of age are already nonambulatory
- Cardiac abnormalities are much more common in nonambulatory participants ≥17 years of age
- NSAD scores decrease in older ambulatory and nonambulatory participants, suggestive of disease progression with age; scores are substantially lower in ambulatory participants ≥17 years of age compared to those 4–7 years of age

Future longitudinal analysis of functional performance of enrolled participants will help support a better interpretation of functional outcomes in clinical trials for LGMD subtypes 2E/R4, 2D/R3, and 2C/R5

Acknowledgments & Disclosures

Acknowledgments: The authors and Sarepta Therapeutics, Inc., thank the participants and their families. Study SRP-LGMD-501-NHS (NCT04475926) was funded by Sarepta Therapeutics, Inc. Editorial support was provided by Hailey Batman, PharmD, of Eloquent Scientific Solutions and was funded by Sarepta Therapeutics, Inc.

Disclosures: LPL, LNA: Received fees from Sarepta Therapeutics, Inc., for licensure of the LGMD natural history data set. Participated on advisory boards of Sarepta Therapeutics. Nationwide Children's Hospital received salary support. **COG:** Participated on advisory boards of Sarepta Therapeutics, Inc., Sanofi, and PTC Therapeutics. **KGC:** Received speaker/advisory board honoraria from Alexion, Alnylam, Amicus Therapeutics, argenx, Biogen, CSL Behring, Ipsen, Janssen Pharmaceuticals, Lupin, Pfizer, Roche, Sanofi Genzyme, and UCB, and research funding from CSL Behring and Roche. **CGL:** Participated in advisory boards for Sarepta Therapeutics, Inc., Dyne, Biogen, Novartis, and Catalyst. **AG:** Received speaker honoraria from PTC Therapeutics. **CMP:** Participated on advisory boards and as a consultant for Biogen, Sarepta Therapeutics, Inc., Novartis Gene Therapies, Genentech/Roche, and Scholar Rock. Served as a speaker for Biogen. Principal investigator of studies sponsored by Novartis Gene Therapies, Astellas, Biogen, Biohaven, CSL Behring, FibroGen, PTC, Pfizer, Sarepta, and Scholar Rock. **JDM:** Participated in advisory boards for Sarepta Therapeutics, Inc., Sanofi, Amicus, Astellas, Spark, and Lupin, and received funding for research from Sanofi, Sarepta, Boehringer Ingelheim, and Spark. **MKJ:** Served on scientific advisory boards for Sarepta, Roche, Pfizer, and Genethon, and has received fees for consulting and training services for PTC, Sarepta, Italfarmaco, Dyne, Pfizer, Summit, Catabasis, Capricor, Santhera, Amicus, NS Pharma, Antisense, Edgewise, and BridgeBio. **HS, LY:** Employees of Sarepta Therapeutics, Inc., and may own stocks in the company. **GC:** Participated on advisory boards and as a consultant for Sarepta Therapeutics, Inc., Italfarmaco, and Roche. Served as a speaker for Sarepta Therapeutics, Inc. Principal investigator of studies sponsored by Sarepta Therapeutics, Inc., Atamyo, Scholar Rock, and Roche.

References

1. National Institutes of Health. Genetic and Rare Diseases Information Center. Limb-girdle muscular dystrophy. https://rarediseases.info.nih.gov/diseases/6907/limb-girdle-muscular-dystrophy. Accessed June 5, 2024. **2.** Murphy AP, Straub V. *J Neuromuscul Dis.* 2015;22:S7-S19. **3.** Moore SA, et al. *J Neuropathol Exp Neurol.* 2006;65:995-1003. **4.** Semplicini C, et al. *Neurology.* 2015;84:1772-81.

SCAN THE QR CODE

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Presented at the 29th Annual Congress of the World Muscle Society
October 8–12, 2024
Prague, Czech Republic