#1212 Safety, β-Sarcoglycan Expression, and Functional Outcomes Following Bidridistrogene Xeboparvovec Treatment in Patients With LGMD2E/R4: VOYAGENE 18-Month Results

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Introduction: Limb-girdle muscular dystrophy 2E/R4 (LGMD2E/R4) is caused by pathogenetic variants in the beta-sarcoglycan (*SGCB*) gene leading to muscle loss. Bidridistrogene xeboparvovec, an adeno-associated virus vector that delivers the full-length SGCB transgene, has shown biologic efficacy and an acceptable safety profile.
Objectives: To present VOYAGENE (SRP-9003-102; NCT05876780) 18-month data evaluating bidridistrogene xeboparvovec treatment in ambulatory and nonambulatory participants with LGMD2E/R4.
Methods: Six participants (aged 17–29 years; 1 ambulatory and 5 nonambulatory; 2 females) received a single infusion of $7.41x10^{13}$ vg/kg bidridistrogene xeboparvovec. Primary endpoints were treatment-emergent adverse events (TEAEs) and day 60 SGCB expression in muscle biopsy via immunofluorescence (IF) and Western blot (WB). Secondary endpoints were day 60 muscle vector genome copies, North Star Assessment for LGMD (NSAD), and Performance of Upper Limb (PUL) 2.0 scores by month 60. Other endpoints included changes in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and creatine kinase (CK) levels through month 60.
Results: No serious TEAEs, discontinuations, or deaths were noted. All participants had TEAEs; most were grade 1 (n=87/153) or 2 (n=63/153), with mostly mild/moderate treatment-related TEAEs (grade 1–2: 40/43; grade 3 [severe]: 3/43). At day 60, muscle biopsy showed increases in SGCB-positive fibers by IF and expression by WB; vector genome DNA was detected in myofibers in all participants. Over time NSAD, PUL 2.0, FVC, and FEV_1 remained stable and participants had reduced CK levels.
Conclusions: These findings show partial restoration of SGCB expression after bidridistrogene xeboparvovec treatment in ambulatory and nonambulatory LGMD2E/R4 individuals.
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Disclosures: AMC has served on an advisory board for Sarepta Therapeutics, Inc., unrelated to this work. MPC, AH, JTA, PL, TF, LRR-K, OR, and HS are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. RSF has served on an advisory board and on a data safety and monitoring board for Sarepta Therapeutics, Inc., unrelated to this work.

#1170 JOURNEY MRI Sub-Study: Baseline Characteristics of Limb-Girdle Muscular Dystrophies 2E/R4, 2D/R3, 2C/R5

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Introduction: Sarcoglycanopathies, accounting for ~15% of limb-girdle muscular dystrophies (LGMDs), are characterized by loss of healthy muscle fibers. However, data on the natural history of LGMDs are limited.
Objectives: To evaluate skeletal muscle magnetic resonance imaging (MRI) in a subset of participants from JOURNEY (NCT04475926), a global, prospective, longitudinal study of the natural history of participants with LGMD2E/R4, 2D/R3, 2C/R5, and 2A/R1.

Methods: MRI was used to characterize skeletal muscle structure and physiology in patients with a sarcoglycanopathy subtype (2E/R4, 2D/R3, 2C/R5).

Results: As of February 2025, baseline MRI data were available for 55 participants; 60.0% were female, and 61.8% were ambulant at baseline. The mean (SD) age was 19.4 (12.89) years for ambulatory participants and 25.5 (14.31) years for nonambulatory participants. For those with data available, lean muscle volume (LMV) was consistently higher in ambulatory participants compared with nonambulatory participants across LGMD subtypes and muscle groups (deltoid, anterolateral lower leg, and quadriceps). Muscle fat fraction (MFF) was generally higher in older ambulatory participants across LGMD subtypes and muscle groups and was highest in nonambulatory participants. Quadriceps generally had the highest mean LMV and MFF values among the muscle groups in both ambulatory and nonambulatory participants.

Conclusions: Overall, baseline muscular MRI data in a subset of JOURNEY participants indicate a more progressed degeneration of affected muscles in older and/or nonambulatory individuals, compared with ambulatory individuals with subtypes R4/2E, R3/2D, and R5/2C. These results support further investigation of muscle MRI as a potential endpoint in LGMD clinical trials.

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#1210 Long-Term Safety and Tolerability of Casimersen Treatment in Patients With Advanced DMD

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Introduction: In study 4045-101 (NCT02530905), casimersen demonstrated safety and tolerability in patients with Duchenne muscular dystrophy (DMD) amenable to exon 45 skipping, which represents about 8% of all patients with DMD.

Objectives: To evaluate the safety and tolerability of casimersen treatment in patients with advanced DMD for up to 6 years as observed in the open-label long-term extension (LTE) study (study 4045-302; NCT03532542) and study 4045-101.

Methods: Patients with advanced DMD (defined as nonambulatory or unable to walk ≥300 meters on the 6-minute walk test) were enrolled in study 4045-101. Patients who completed study 4045-101 were included in the LTE and continued receiving casimersen 30 mg/kg intravenous infusion once weekly. Adverse events, clinical laboratory tests, and cardiac assessments were monitored.

Results: Of the 12 patients enrolled in study 4045-101, 11 (91.7%) continued in study 4045-302. The mean (SD; range) duration on treatment was 5.7 (0.99; 2.5-6.2; n=12) study years. Throughout both studies, treatment-emergent adverse events (TEAEs) were generally mild (87%), unrelated to treatment (97%), and decreased during the LTE. Over 6 study years, four patients experienced 14 serious TEAEs; none were related to treatment. The most common TEAEs were nasopharyngitis (75%), headache (58%), and cough (50%). No patterns or trends in hematology, coagulopathy, chemistry, or other clinical laboratory parameters were observed. During the LTE study, no discontinuations, port-related infections, or dosage reductions were reported, and no casimersen-related cardiac or kidney toxicity signals were identified.

Conclusions: Over 6 study years, casimersen was well tolerated and demonstrated a manageable safety profile, consistent with previous clinical and real-world experience, supporting the use of casimersen in patients with advanced DMD.

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