#P223

Long-Term Safety of Bidridistrogene Xeboparvovec After 5-Year Follow-Up From a Phase 1/2 Trial

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Background

- Limb-girdle muscular dystrophy 2E/R4 (LGMD2E/R4) is caused by mutations in the β-sarcoglycan (*SGCB*) gene, leading to SGCB deficiency and consequent muscle loss[1]
- Bidridistrogene xeboparvovec, a recombinant adeno-associated virus serotype rh74 (rAAVrh74) vector containing the *SGCB* transgene, is designed to be delivered to skeletal and cardiac muscle of subjects with confirmed diagnosis of LGMD2E/R4[1]
- Here we report long-term safety over a 5-year follow-up from a phase 1/2 study of bidridistrogene xeboparvovec (NCT03652259, SRP-9003-101)[2]

Objective

To report the long-term treatment-related safety from patients treated with bidridistrogene xeboparvovec in Study 101 cohort 1 (5 years) and cohort 2 (4 years)

Methods

- Patients aged 4 to 15 years with *SGCB* mutations at both alleles were eligible to enroll
- At baseline, all patients were negative for antibodies against AAVrh74 and scored ≥40% of normal on the 100-meter timed test
- Patients received bidridistrogene xeboparvovec as a single one-time intravenous dose of 1.85×10^{13} vg/kg (cohort 1) or 7.41×10^{13} vg/kg (cohort 2)
- The primary endpoint was to evaluate safety of bidridistrogene xeboparvovec

Conclusions

Patients treated with bidridistrogene xeboparvovec demonstrated an acceptable long-term safety profile with over 4- to 5-year follow-up, with the majority of TR-TEAEs occurring within 90 days post infusion

Further confirmation is needed with larger sample sizes from pivotal studies

Results

- Patient demographics are summarized in **Table 1**

Table 1 *Summary of Demographics*

Parameter	Cohort 1 (n=3)	Cohort 2 (n=3)	Total (N=6)
Dose	1.85×10^{13} vg/kg	7.41×10^{13} vg/kg	
Gender, n (%)			
Male	1 (33.3)	2 (66.7)	3 (50.0)
Female	2 (66.7)	1 (33.3)	3 (50.0)
Age, years			
Mean (SD)	10.0 (5.20)	10.0 (1.73)	10.0 (3.46)
Median	13.00	11.00	11.00
Min, max	4, 13	8, 11	4, 13
Weight, kg			
Mean (SD)	42.3 (21.39)	32.1 (6.52)	37.2 (15.22)
Median	53.10	29.40	34.45
Min, max	18, 56	27, 40	18, 56

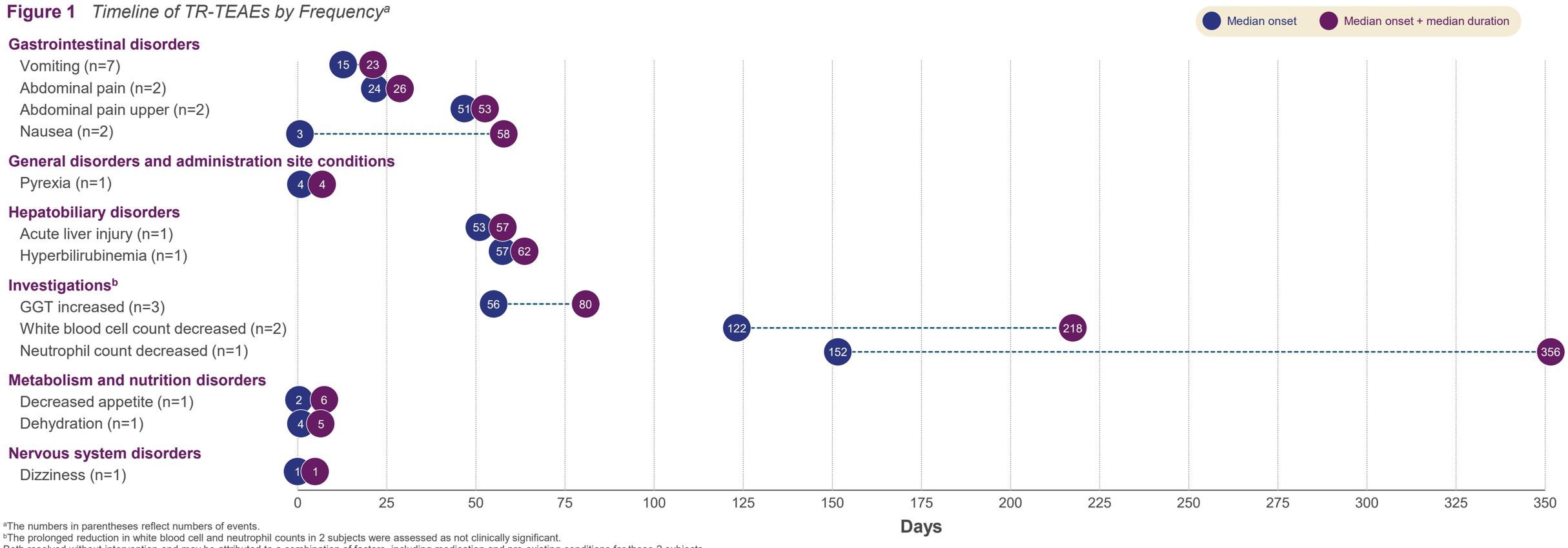
- The most common treatment-related treatment-emergent adverse events (TR-TEAEs) included vomiting, gamma-glutamyl transferase (GGT) increase, abdominal pain, upper abdominal pain, nausea, and decreased white blood cell count (**Table 2**)
  - Among the 25 TR-TEAEs, the majority were mild (13 of 25) or moderate (10 of 25) in severity, and 2 (of 25) were severe
- The most common TR-TEAEs (≥10%) occurred within 90 days post infusion and included vomiting and increased GGT (**Figure 1**)
  - All TR-TEAEs resolved with clinical care and conservative management and did not recur
- 1 patient experienced severe dehydration on day 4 that resolved on day 5, after they received outpatient care (**Figure 1**)
- Acute liver injury was severe and deemed related to study treatment (days 53–57) (**Figure 1**)
  - The patient was hospitalized, and the adverse event (AE) resolved
- Cardiomyopathy (grade 3) was assessed as related to LGMD and not related to treatment (days 487–490)
  - The patient was hospitalized, and the AE resolved
- No patient met the prespecified elevation in GGT levels criteria for acute liver injury, and no patient was diagnosed with thrombocytopenia
- There were 2 patients who experienced alanine transaminase and aspartate transaminase (AST) levels greater than 3× the upper limit of normal (ULN) in cohort 1
  - 1 patient experienced AST levels above the threshold of 3× the ULN in cohort 2

Table 2 *Summary of Patients With TR-TEAEs by System Organ Class Preferred Term*

System Organ Class Preferred Term, n (%)	Cohort 1 (1.85×10^{13} vg/kg) (n=3)	Cohort 2 (7.41×10^{13} vg/kg) (n=3)	Total (N=6)
Any TR-TEAE	2 (66.7)	3 (100)	5 (83.3)
Gastrointestinal disorders	1 (33.3)	3 (100)	4 (66.7)
Vomiting	1 (33.3)	3 (100)	4 (66.7)
Abdominal pain	0	2 (66.7)	2 (33.3)
Abdominal pain upper	1 (33.3)	1 (33.3)	2 (33.3)
Nausea	0	2 (66.7)	2 (33.3)
General disorders and administration site conditions	0	1 (33.3)	1 (16.7)
Pyrexia	0	1 (33.3)	1 (16.7)
Hepatobiliary disorders	1 (33.3)	0	1 (16.7)
Acute liver injury	1 (33.3)	0	1 (16.7)
Hyperbilirubinemia	1 (33.3)	0	1 (16.7)
Investigations	2 (66.7)	3 (100)	5 (83.3)
GGT increased	2 (66.7)	1 (33.3)	3 (50.0)
White blood cell count decreased	0	2 (66.7)	2 (33.3)
Neutrophil count decreased	0	1 (33.3)	1 (16.7)
Metabolism and nutrition disorders	1 (33.3)	1 (33.3)	2 (33.3)
Decreased appetite	1 (33.3)	0	1 (16.7)
Dehydration	0	1 (33.3)	1 (16.7)
Nervous system disorders	1 (33.3)	0	1 (16.7)
Dizziness	1 (33.3)	0	1 (16.7)

GGT=gamma-glutamyl transferase; TR-TEAE=treatment-related treatment-emergent adverse event.

Figure 1 *Timeline of TR-TEAEs by Frequency*[a]



[a]The numbers in parentheses reflect numbers of events.
[b]The prolonged reduction in white blood cell and neutrophil counts in 2 subjects were assessed as not clinically significant. Both resolved without intervention and may be attributed to a combination of factors, including medication and pre-existing conditions for these 2 subjects.

GGT=gamma-glutamyl transferase; TR-TEAE=treatment-related treatment-emergent adverse event.

References

1. Mendell JR, et al. *Nat Med*. 2024;30(1):199-206. **2.** ClinicalTrials.gov. NCT036559.

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Disclosures: JRM: Received study funding from Sarepta Therapeutics, Inc., while at Nationwide Children's Hospital at the time of the study and is currently an employee of Sarepta Therapeutics, Inc. **AMC:** Has served on an advisory board for Sarepta Therapeutics, Inc., unrelated to this work. **ZS:** Received grant support from Sarepta Therapeutics, Inc., and the Parent Project Muscular Dystrophy. **LHC:** Received grant support from and is a consultant for Sarepta Therapeutics, Inc., unrelated to this work. **KH:** Is a consultant for Sarepta Therapeutics, Inc., unrelated to this work. **ECB:** Has nothing to disclose. **WH, HS, PL**, and **LR-K:** Employees of Sarepta Therapeutics, Inc., and may own stock/options in the company.

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