

Evaluation of Total Binding Antibodies Against rAAVrh74 in Patients With Duchenne Muscular Dystrophy



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Objective

Determine the prevalence of individuals with elevated rAAVrh74 total binding antibodies in a Duchenne muscular dystrophy (DMD) population

Key Takeaways

Low seroprevalence of antibodies against rAAVrh74 supports the broad applicability of rAAVrh74-based gene transfer therapy to patients with DMD

CONCLUSIONS

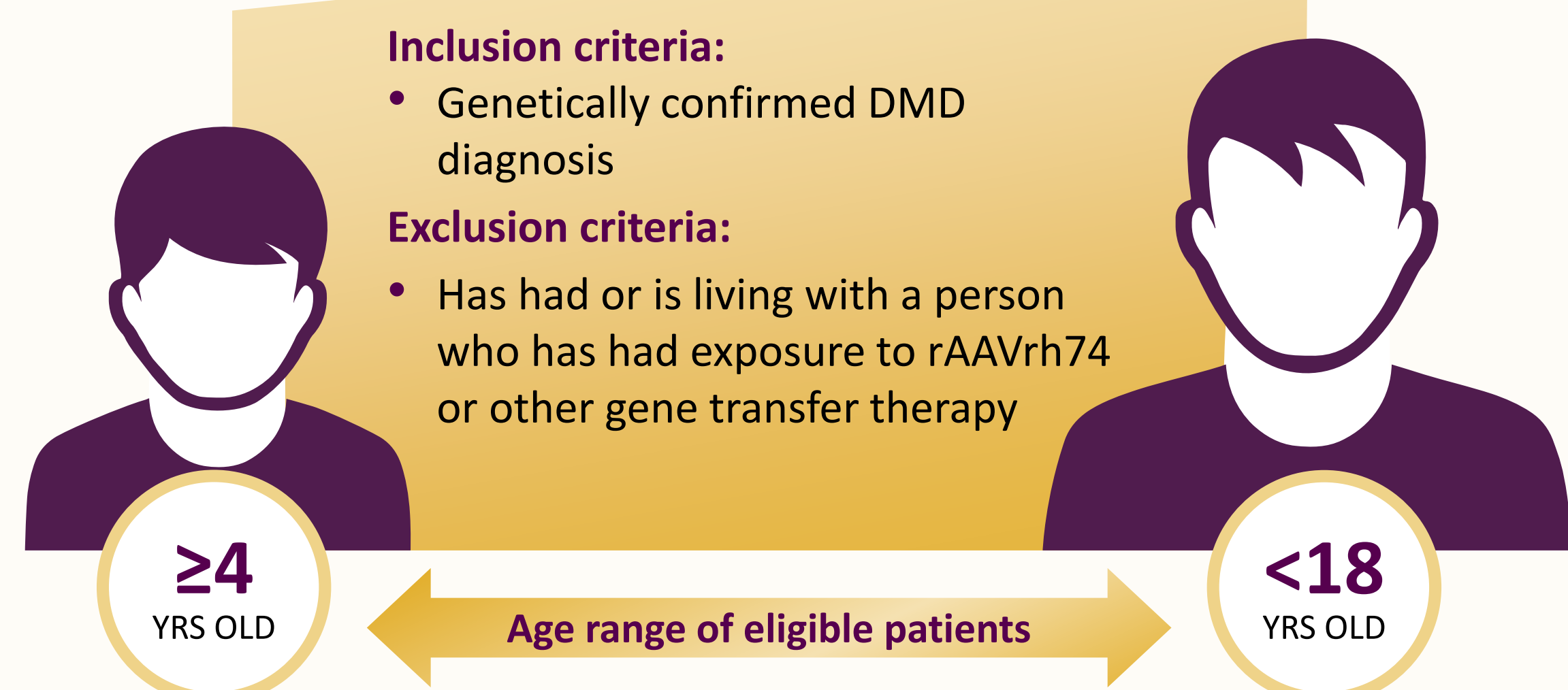
- The majority (86.1%) of patients with DMD in this dataset were seronegative (titer <1:400) for anti-rAAVrh74 total binding antibodies; these subjects would be eligible for entry into currently enrolling rAAVrh74-based clinical trials for DMD
- The comprehensive approach of measuring total binding antibodies (both neutralizing and non-neutralizing) may improve the safety and efficacy of AAV-based gene therapy treatments⁵

BACKGROUND

- Adeno-associated virus (AAV) vectors have emerged as the vehicle of choice for gene transfer therapy for DMD and limb-girdle muscular dystrophy, as they can be delivered systemically, are nonpathogenic, and exhibit broad tissue tropism¹
- rAAVrh74 serotype efficiently transduces skeletal and cardiac muscle following intravenous administration
- Since it's derived from rhesus monkeys, rAAVrh74 is less likely to be associated with pre-existing immunity compared with serotypes isolated from humans²
- Because pre-existing antibodies against AAV vectors can hamper therapeutic efficacy and pose a safety concern,^{3,4} successful gene transfer requires patient pre-screening; those seropositive for total anti-rAAVrh74-binding antibodies may not be eligible for gene therapy
- Here, we present results of a study evaluating total binding antibodies against rAAVrh74 in 101 patients with DMD

STUDY DESIGN

Planned sample size: N=100

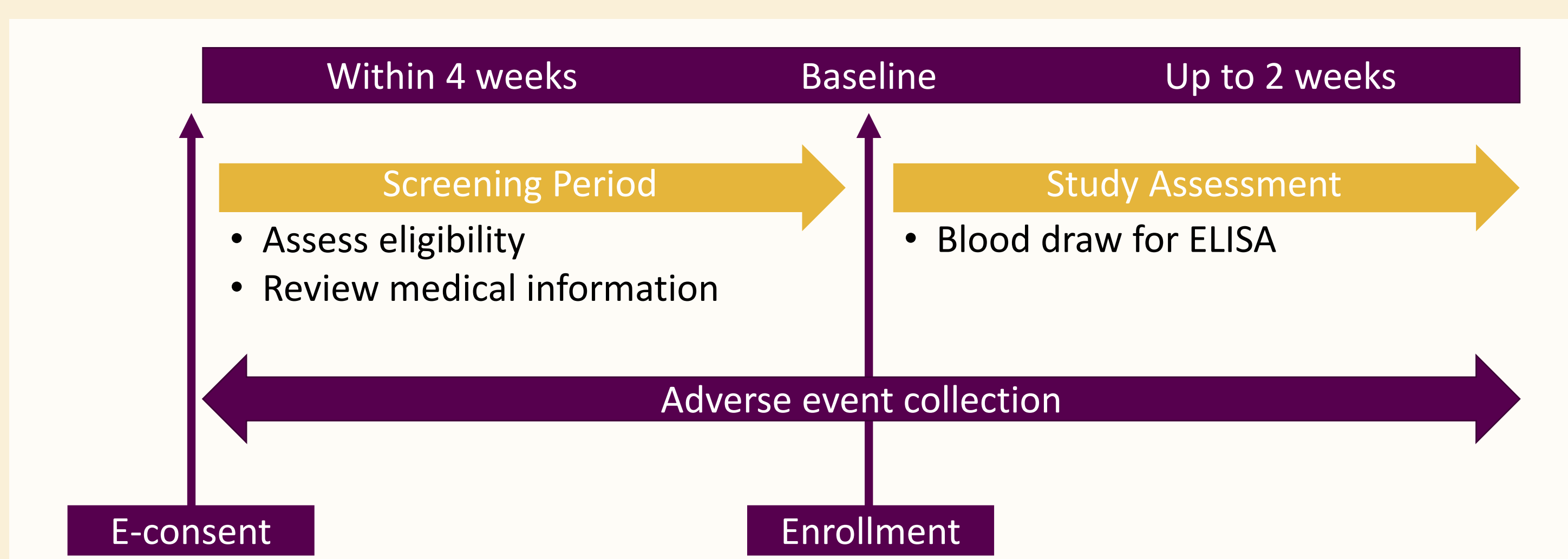


Procedures

- The study design was virtual to lower the study burden on patients, caregivers, and healthcare providers
- A single blood sample was obtained from each patient either via home phlebotomy or at a patient service center, and total anti-rAAVrh74-binding antibodies were measured by enzyme-linked immunosorbent assay (ELISA)
 - Total anti-AAV antibodies include both neutralizing antibodies, which prevent transduction of the vector, and non-neutralizing antibodies, which recognize the vector and may cause immune-mediated effects⁵

Total binding antibodies (non-neutralizing + neutralizing)

Neutralizing antibodies



Endpoints

- Primary: Percentage of subjects with elevated ($\geq 1:400$) total antibody titers to rAAVrh74
 - Total binding antibody level <1:400 was defined as “not elevated”
 - Clinically validated cutoff was selected based on a previous study showing that antibody titers at 1:800 promoted loss of transgene expression⁶

RESULTS

Patients

- Out of 107 patients enrolled, 101 patients had at least 1 sample evaluated with a valid result for immunogenicity (full analysis set) and completed the study
- The option for home phlebotomy was selected by 81% of patients

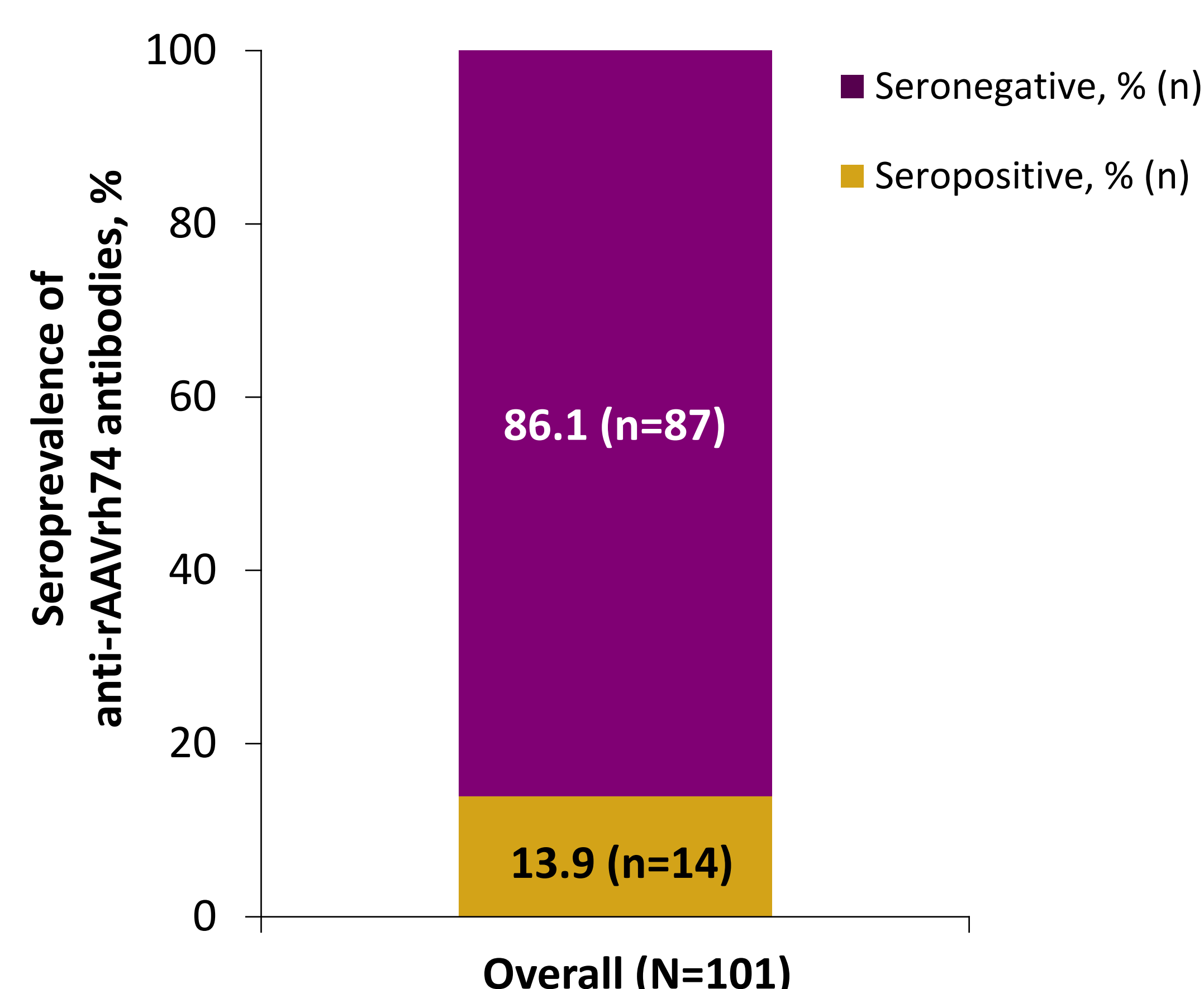
Baseline characteristics of study participants (N=101)

Parameter	Mean Years (SD)
Age	9.1 (3.5)
Years since 1st motor symptom of DMD to study enrollment ^a	6.2 (3.6)
Years since diagnosis of DMD to study enrollment ^b	5.5 (3.5)
Years since the confirmatory genetic testing for DMD to study enrollment	5.3 (3.5)
Race	n (%)
White	79 (78)
Other	22 (22)

^an=94; ^bn=99. SD, standard deviation. Percentages may not sum to 100 due to rounding.

Total antibody titers to rAAVrh74

- Overall, 87/101 (86.1% [95% CI: 77.8, 92.2]) patients did not have pre-existing elevated ($\geq 1:400$) total antibody titers to rAAVrh74



Range of total antibody titers to rAAVrh74

- In the 14 patients with elevated anti-rAAVrh74 antibodies, titers ranged from 1:400 to 1:3200

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