

# Lower POLARIS-101™ (AAV-SLB101) Cross-Reactive Antibodies in Elevidys-treated Patients

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## INTRODUCTION

### Background:

- POLARIS-101™ is a rationally engineered AAV capsid with unique properties including reduced cross-reactive antigenicity.
- Elevidys is an FDA-approved (2023) AAVrh74-based gene therapy delivering a microdystrophin for Duchenne muscular dystrophy.
- AAV gene therapy induces robust humoral immune responses against the capsid, including neutralizing (NAb) and binding antibodies (TAb), which may impact eligibility for subsequent dosing.
- Cross-reactive antibodies across AAV capsid serotypes have been reported following treatment, representing a potential barrier to redosing or use of alternate capsids.
- Characterizing cross-reactive antibody profiles in previously treated patients is important to assess the feasibility of alternative capsids for future dosing strategies.

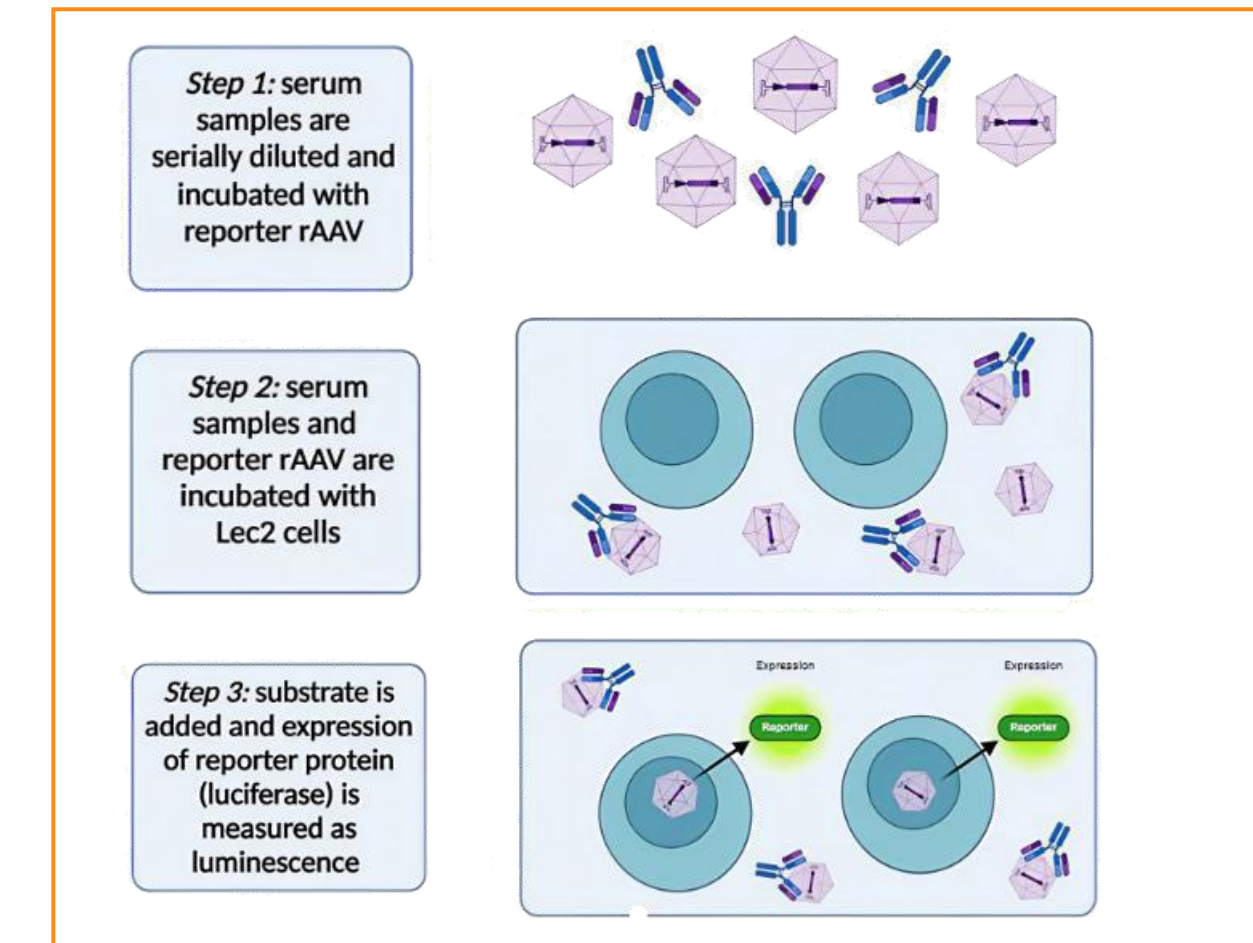
### Approach:

- Human serum samples (n=11) were obtained from CureDuchenne (n=6) and Edgewise Therapeutics (n=5).
- Samples were derived from Duchenne patients with prior exposure to AAV gene therapy (treatment history not fully confirmed).
- Neutralizing antibody (NAb) titers against AAVrh74, AAV8, and POLARIS-101 were measured; titers <1:5 were considered negative.
- Total anti-AAV IgG (TAb) titers against AAVrh74 and POLARIS-101 were measured; titers <1:25 were considered negative.
- AAV8 TAb assays were not included due to ongoing assay development.
- Patients were stratified post hoc based on relative antibody reactivity profiles, with elevated AAVrh74 titers used as a surrogate indicator of prior AAVrh74 exposure.

## ASSAY METHODOLOGY

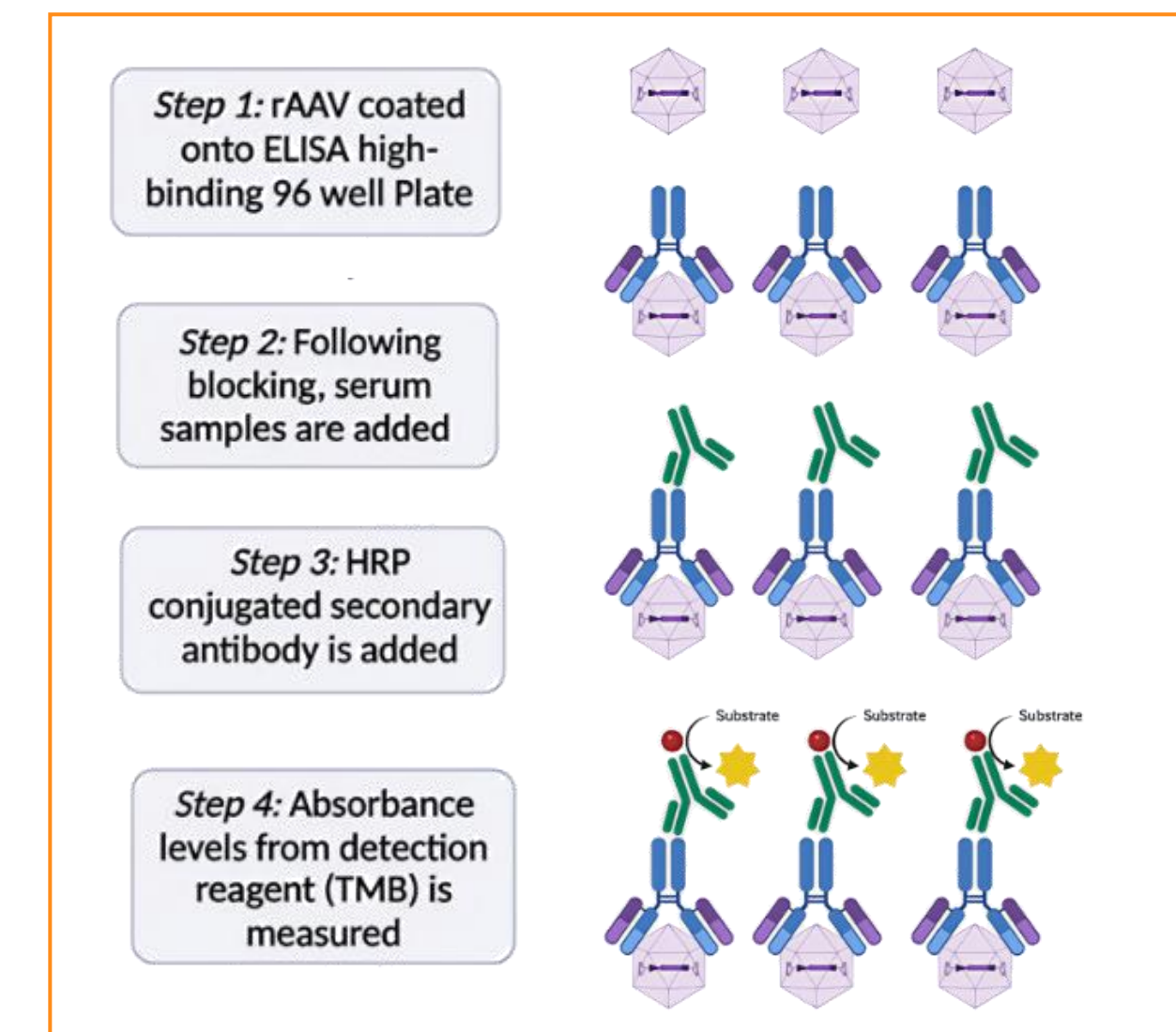
### Neutralizing Antibody (NAb) vs Total Antibody (TAb) Assay

#### A. Cell Based NAb Assay



A cell-based transduction inhibition assay and a plate-based modified ELISA assay were used to quantify (A) neutralizing (NAb) and (B) binding (TAb) antibodies against capsid serotypes. NAb assay considers all neutralizing factors, including antibodies while the TAb assay measures specifically IgG.

#### B. Plate Based IgG TAb Assay



### AAV clades



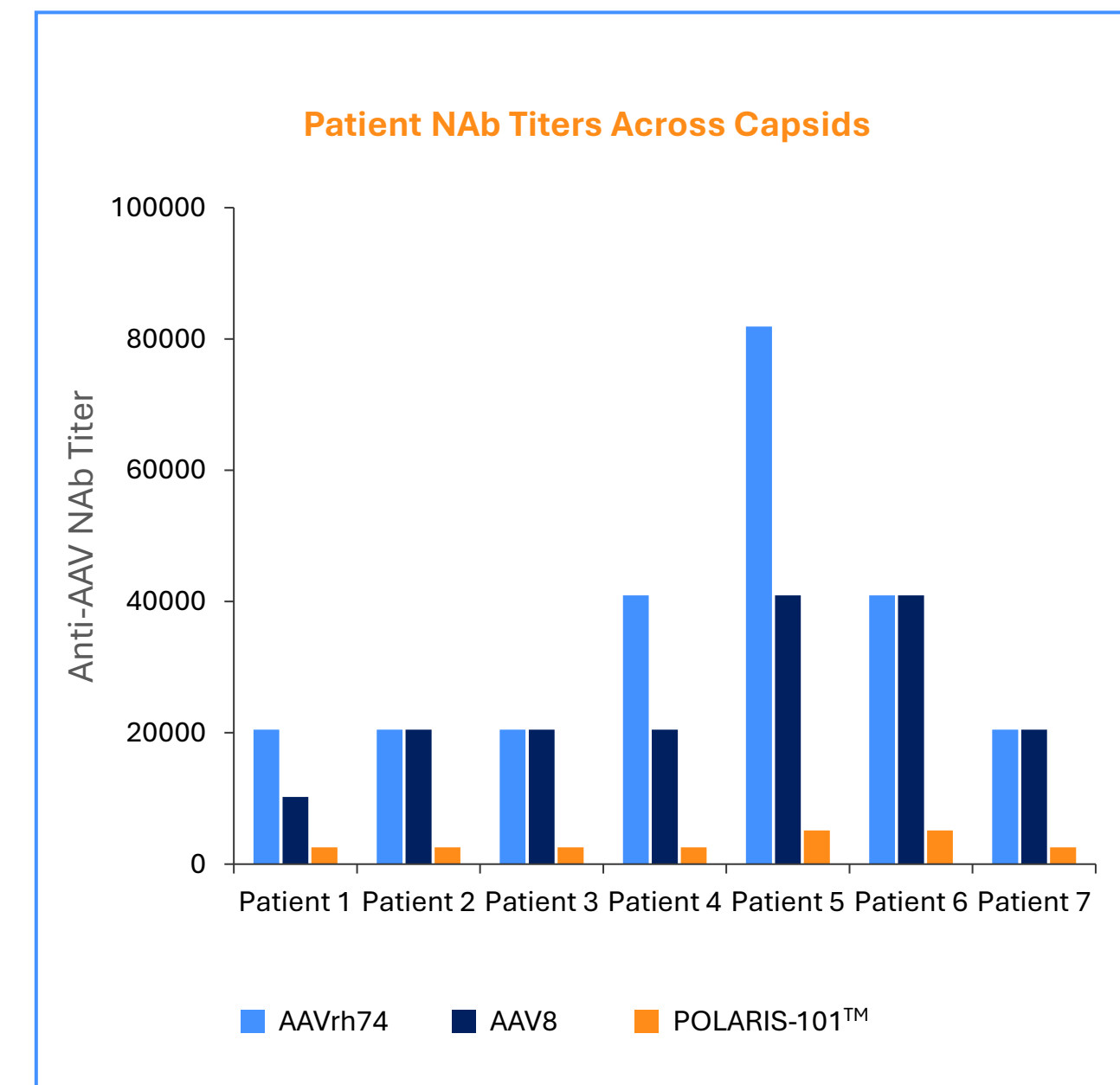
- AAVrh74 → clade E
- AAV8 → clade E
- POLARIS-101™ → clade F

## LOWER POLARIS-101™ NAb TITERS FOLLOWING ELEVIDYS TREATMENT

POLARIS-101™ Shows ~10-Fold Lower NAb Titers vs AAVrh74 in Elevidys-Exposed Sera

Table 1. Anti-AAV NAb titers per capsid

Patient	AAVrh74	AAV8	POLARIS-101™
1	1:20480	1:10240	1:2560
2	1:20480	1:20480	1:2560
3	1:20480	1:20480	1:2560
4	1:40960	1:20480	1:2560
5	1:81920	1:40960	1:5120
6	1:40960	1:40960	1:5120
7	1:20480	1:20480	1:2560



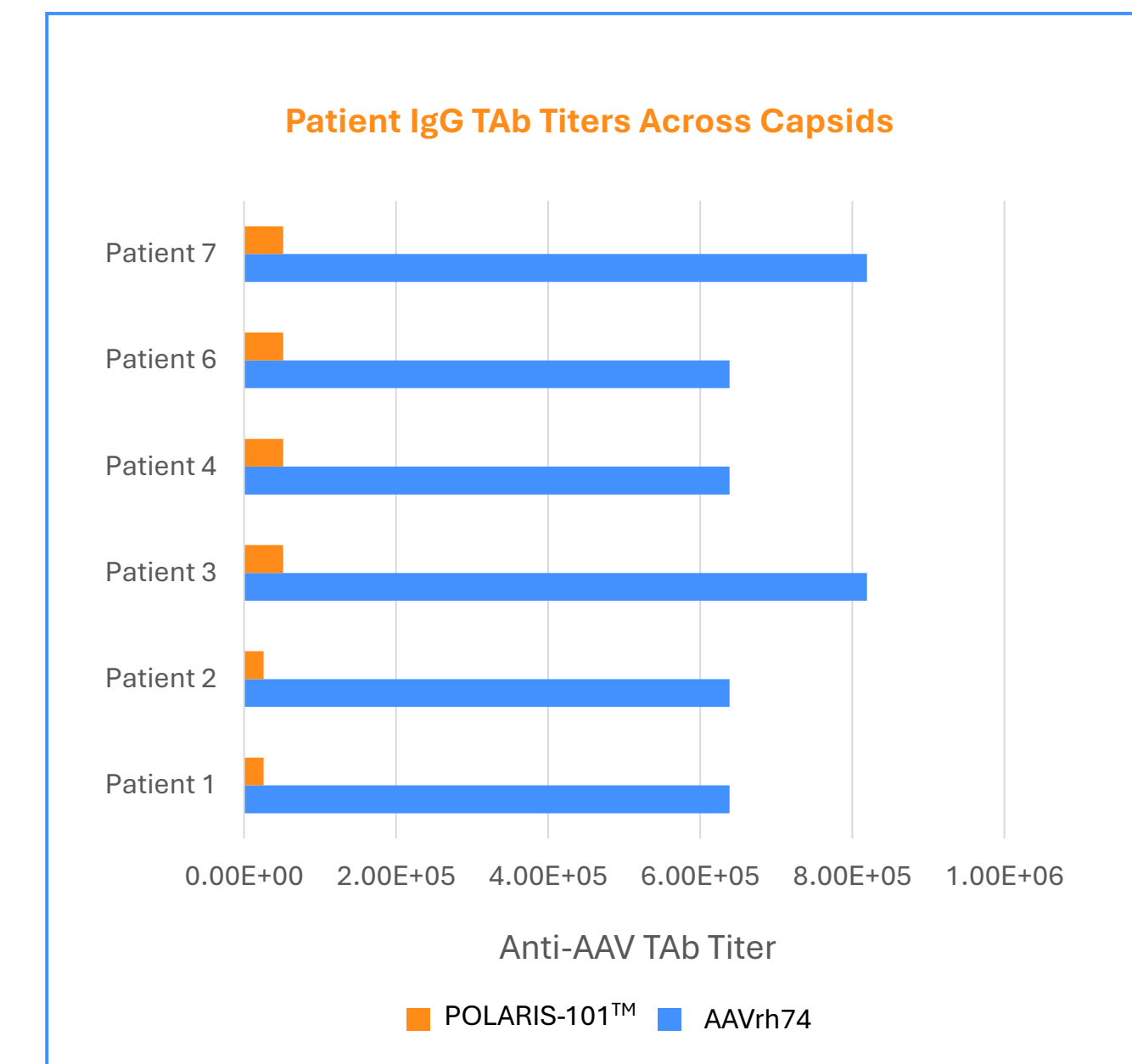
All Elevidys-treated patients had anti-AAVrh74 NAb titers that were >4000x the threshold for sample positivity (<1:5). AAV8 NAb titers were not significantly different from AAVrh74 titers (p=0.68). POLARIS-101™ NAb titers differed significantly (p=0.02) and were on average 10x lower compared to AAVrh74 titers.

## REDUCED POLARIS-101™ IgG TAb TITERS FOLLOWING ELEVIDYS TREATMENT

~POLARIS-101™ shows ~17-Fold Lower TAb titers vs AAVrh74 in Elevidys-Exposed Sera

Table 2. Anti-AAV TAb titers per capsid

Patient	AAVrh74	POLARIS-101™
1	1:638400	1:25600
2	1:638400	1:25600
3	1:819200	1:51200
4	1:638400	1:51200
5	1:638400	1:51200
6	ND*	
7	1:819200	1:51200



TAb titers against AAVrh74 were on average >40,000x the cut off value (<1:25) while titers against POLARIS-101™ were on average ~1600x. AAV8 TAb titers were not analyzed in this study. \*ND -> not determined due to insufficient material.

## CONCLUSIONS

- In a cohort of Duchenne patient sera with prior AAV exposure, antibody responses to POLARIS-101™ were consistently lower than those observed against AAVrh74.
- Neutralizing antibody (NAb) titers to POLARIS-101™ were approximately one order of magnitude lower and total antibody (TAb IgG) titers were substantially reduced relative to AAVrh74.
- In contrast, NAb titers against AAV8 capsid were comparable to AAVrh74, indicating broad cross reactivity against these Clade E AAV capsids.
- The underlying basis for reduced reactivity, including the potential contribution of capsid engineering remains to be further characterized.
- These findings support continued evaluation of POLARIS-101™ in the context of alternative capsid strategies for patients with prior AAV exposure.

### ACKNOWLEDGMENTS

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