Limited by Design: SRP-9001 Approval Unlikely

Summary: DeLT4 predicted regulatory outcomes for SRP-9001 accelerated approval are 85% rejection probability due to lack of efficacy and proximity to EMBARK top-line readout in 4Q23 (PT $100); 15% acceptance probability based on positive AdCom vote (8:6), "lack of alternatives", and efficacy in younger patients (PT $160). Catalyst event regarding accelerated approval is on June 22nd

- **DataChanneling suggests that FDA will not approve SRP-9001 for DMD given** 1) safety signal with >10% of patients showing treatment related SAEs, 2) lack of efficacy, 3) expression of µDystrophin did not correlate with NSAA (poor surrogate endpoint), and 4) episomal vectors lose expression over time in highly regenerative tissues

- **Hyperforecasting sets 90% probability SRP-9001 EMBARK 4Q:23 top-line data readout to show lack of efficacy** (52-week top-line NSAA data by 4Q:23; PT$75). Full-report of Part 1 of EMBARK study in early 2024 not likely a relevant catalyst

- **Safety: SRP-9001 safety profile is not clean enough given lack of efficacy.** 9 out of 85 patients showed SRP-9001 treatment related SAEs, including liver injury and myocarditis. Other DMD gene-therapy trials were paused due to acute kidney disease (SGT-001 from Solid Biosciences) and a patient's death (fordadistrogene movaparvovec from Pfizer)

- **Efficacy: SRP-9001 showed NO statistical significant increase in NSAA score in a placebo controlled study.** Efficacy observed in the 4-5 year old subgroup derived from a gain NSAA score over 4-8 weeks, after which kinetics of disease progression was similar to pbo (low number of patients with n=8 SRP-9001, n=8 pbo). Although EMBARK (-301 study) stratifyes patients by age and NSAA score at baseline, it will likely not be sufficiently powered to achieve stat. sig. given expected 2-point difference in score

- **Surrogate Endpoint: Not appropriate.** Expression of functional Dystrophin should correlate with muscle function, however NO stat. sig. correlation between µDystrophin levels and NSAA score was observed. This could be due to heterogeneous expression (AAV episomal copy number varies, and not all muscle cells carry the vector), or lack of µDystrophin activity in human patients compared to pre-clinical data

- **Design Matters: DMD is a wear-and-tear disease and not all muscles are the same.** Optimal treatment requires 1) a functional Dystrophin construct, 2) early dosing, 3) restoring muscle function AND regeneration, especially in life limiting diaphragm and heart. Dosing 1 year-olds with integrative vectors (LVs) or genome-editors able to recapitulate natural Dystrophin expression would represent a better alternative.