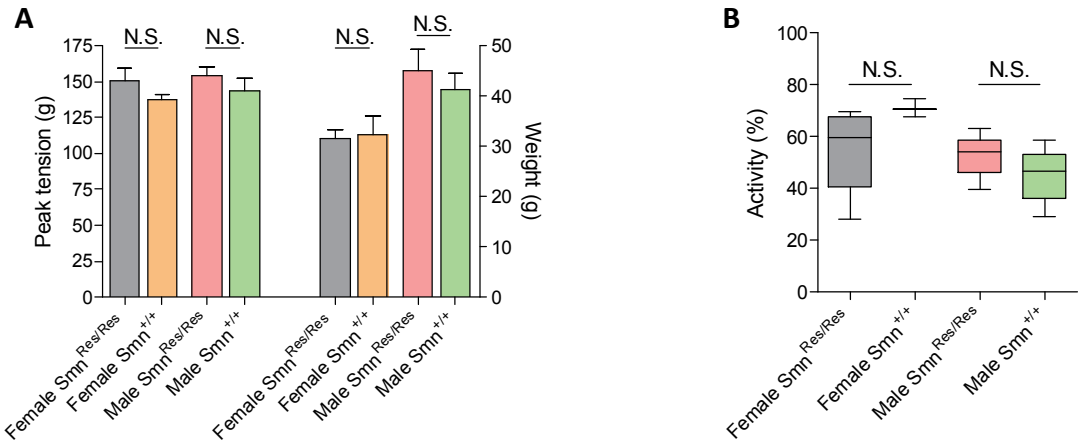
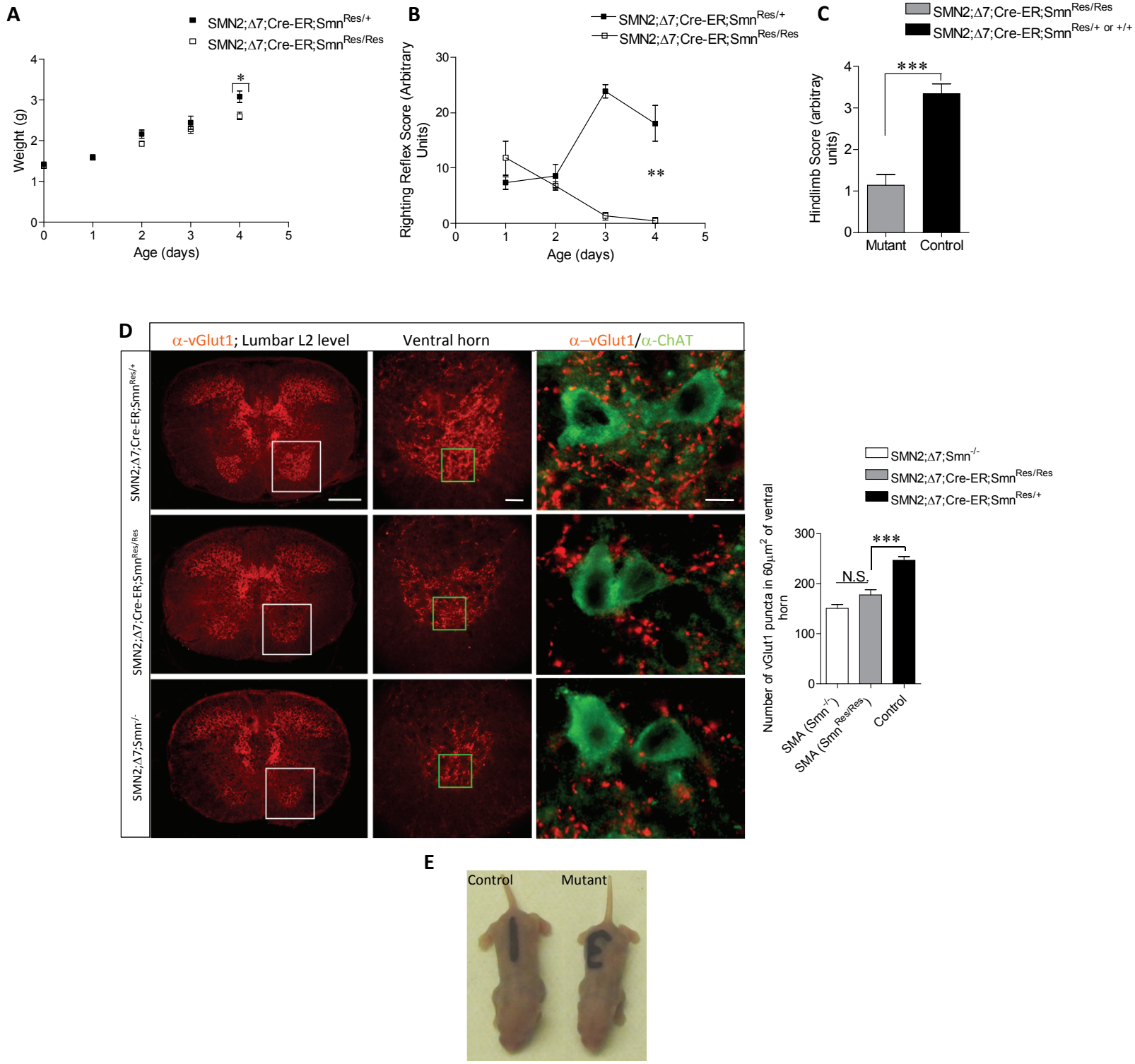
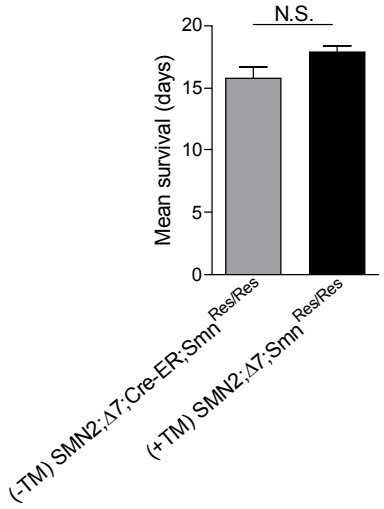


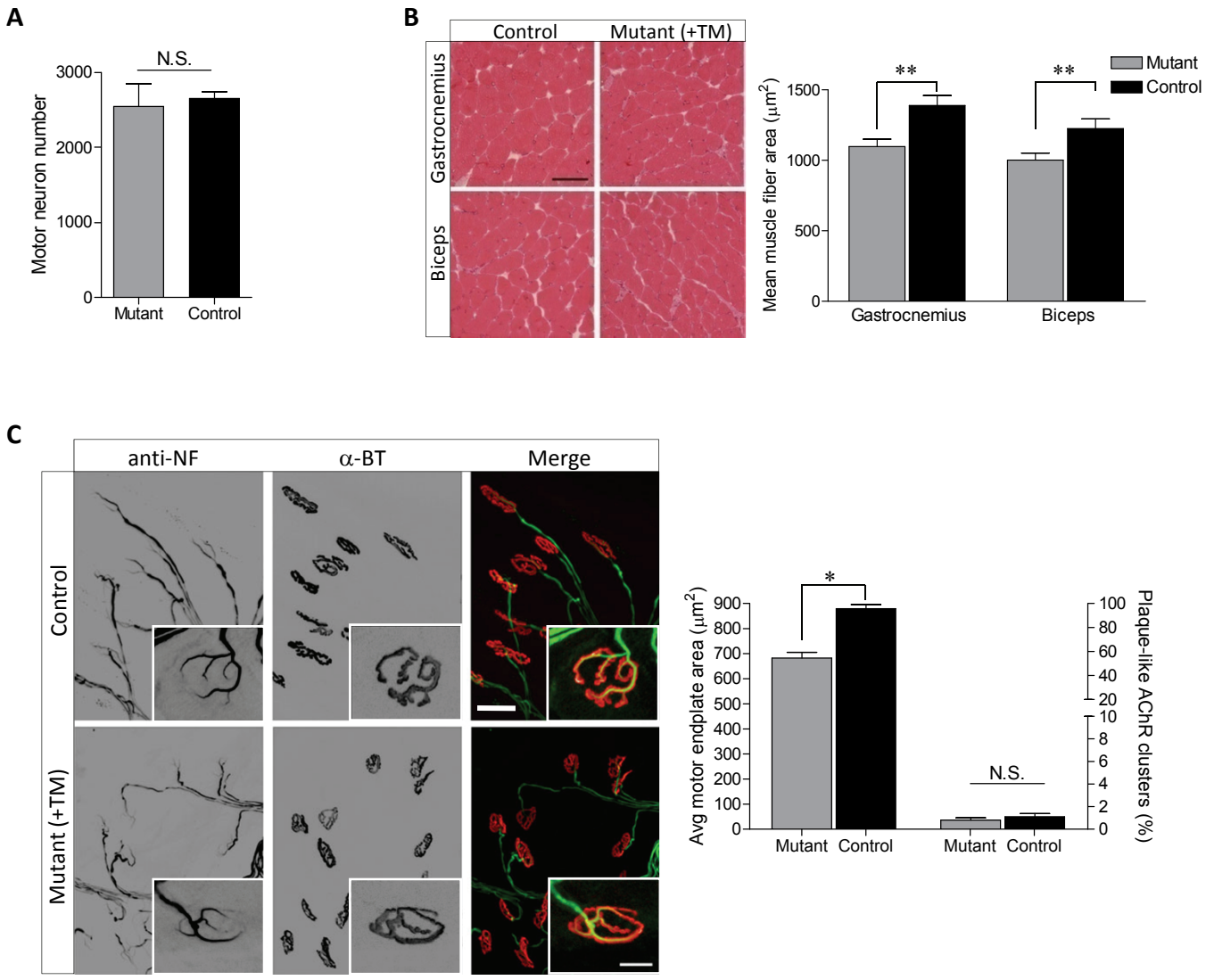
Supplemental Figure 1 - Cre-mediated induction of the *Smn* rescue allele in the germ line confers complete phenotypic correction in model mice. **(A)** Grip strength analysis and body weight measurements of mice carrying the 'active' conformation of the rescue allele relative to those of wild-type littermates are indicative of full phenotypic rescue. Note: As expected, female mice displayed reduced body weight compared to age-matched male animals. **(B)** Activity measurements in an open field assay were indistinguishable between wild-type mice and those homozygous for the flipped rescue allele. Note: n ≥ 5 for each cohort except $Smn^{+/+}$ mice where n = 3. N.S. indicates $P > 0.05$, Student's *t* test.



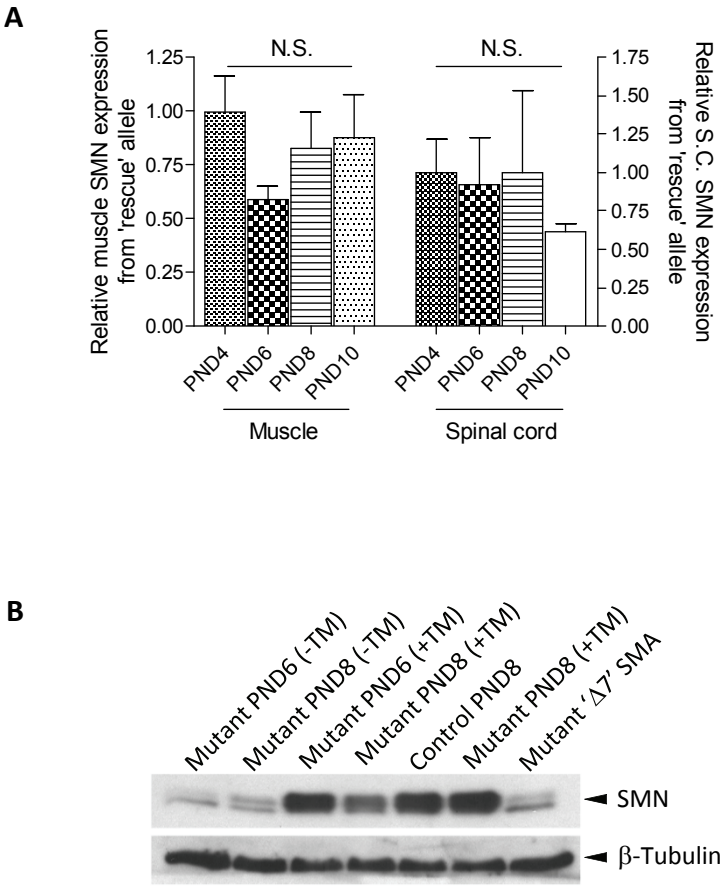
Supplemental Figure 2 - An overt disease phenotype is evident in neonatal mutant mice harboring the 'rescue' allele. Body weight measurements **(A)** indicated that mutants homozygous for the rescue allele were significantly smaller and displayed weakness assessed by **(B)** an impaired righting reflex and **(C)** the hind limb suspension test. Additionally, mutant mice displayed **(D)** fewer proprioceptive vGlut1 puncta in the ventral horn of the spinal cord (Scale bars – left hand panel = 600μm; center panel = 30μm; right hand panel = 8μm), and **(E)** appeared visually smaller than age-matched littermates at PND4. Note: n ≥ 6; $P < 0.05$ (body weight measurements), $P < 0.01$ (righting reflex scores), $P < 0.001$ (tube test and number of vGlut1 puncta); Student's *t* test. Also note: Center panels in **(D)** represent a magnified version of the boxed region in the left hand panels. Regions in the center panels circumscribed by green boxes were used to carry out the quantification of SMN intensity. *SMN2;Δ7;Smn* $^{-/-}$ = 'Δ7' SMA mutant; *SMN2;Δ7;Cre-ER;Smn*$^{Res/Res}$ = 'rescuable' SMA mutant.



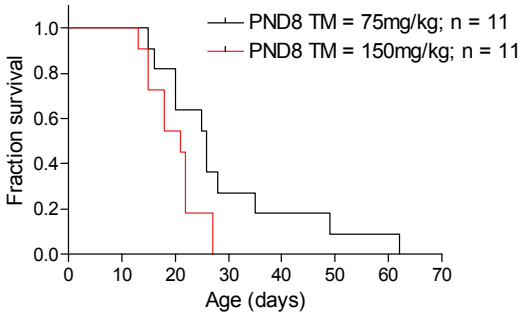
Supplemental Figure 3 - Mean survival of TM treated mutants in the absence of Cre-ER is no different from that of untreated mutants harboring the Cre allele, n ≥ 14, $P > 0.05$, Student's *t* test.



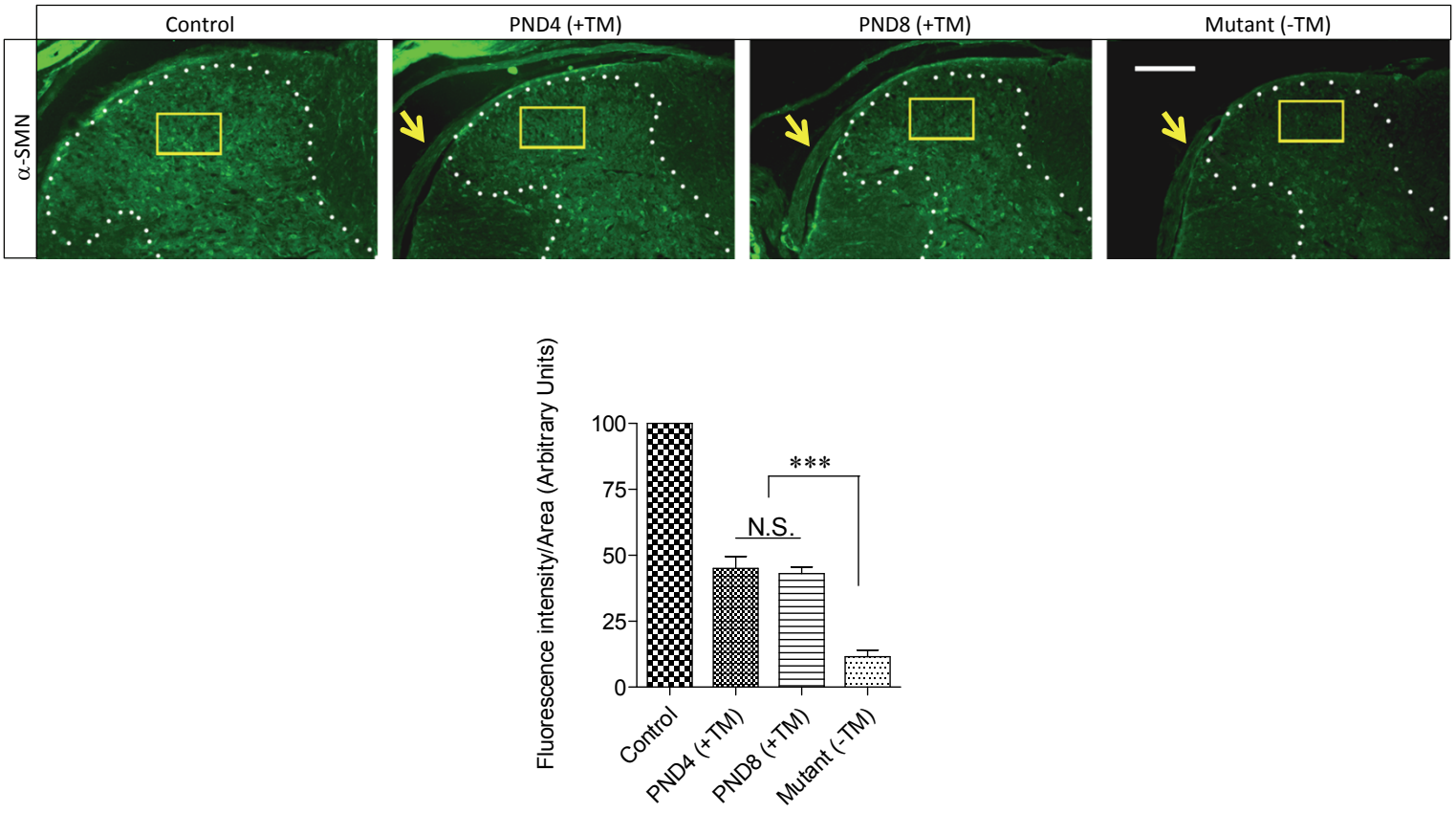
Supplemental Figure 4 - Normal neuromuscular morphology in adult mutants treated as symptomatic neonates. SMN up-regulation at PND4 in symptomatic SMA model mice **(A)** prevents spinal motor neuron degeneration ($P > 0.05$) and **(B)** restores normal muscle morphology in the adult mice. For muscle fiber size, $P < 0.01$ for both gastrocnemius and biceps. Muscle fibers were analyzed in cross section. **(C)** Post-synaptic AChR clusters in adult mutants treated at PND4 appear smaller ($P < 0.01$) but fully developed, pretzel shaped structures which were equivalent in numbers to those of WT controls. Pre-synaptic specializations in mutant muscle appeared free of NF aggregates and appropriately branched into nerve terminals. > 500 NMJs were examined in each of 2 mice per genotype. Scale bars – 100μm **(B)**; 40μm; inset – 20μm **(C)**.



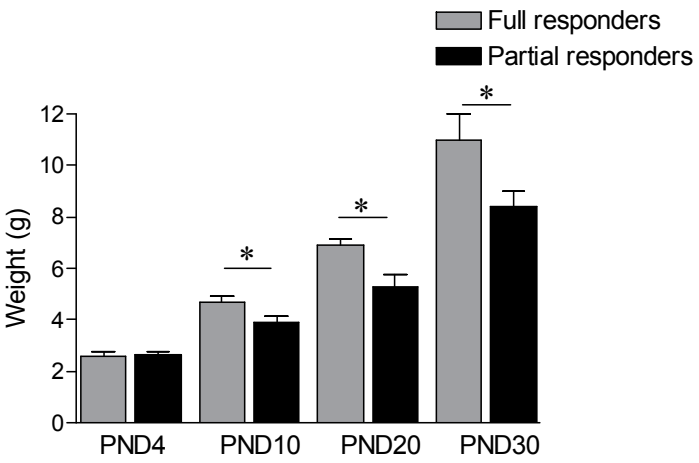
Supplemental Figure 5 – (A) No significant difference in levels of FL-SMN transcript expressed in spinal cord and muscle tissue from mice administered TM at different time points to induce recombination and expression from the rescue allele. n ≥ 4 for each time point except for PND6 where n = 3; $P > 0.05$; one-way ANOVA. **(B)** Western blot analysis of spinal cord tissue from mutant mice *(SMN2;Δ7;Cre-ER;Smn$^{Res/Res}$)* treated with TM at PND4 and analyzed at the specific time points shown exhibit elevated SMN protein as early as 48 hours post-treatment. Control animal is identical in genotype except that it harbors one wild-type *Smn* allele. The 'Δ7' SMA mutant (*SMN2;Δ7;Smn$^{-/-}$)* serves as an additional control.



Supplemental Figure 6 - Increased TM administration at PND8 fails to bring about greater phenotypic rescue of mutants as measured by survival assays. $\chi^2 = 3.79$; $P > 0.05$; log-rank test.



Supplemental Figure 7 – An equivalent increase in SMN levels in the dorsal horns of ~2-week old mutant mice treated at PND4 or PND8. Fluorescence intensity, expressed as % of the controls, was measured in the boxed regions indicated on the photomicrographs. Arrows indicate dorsal roots. Dorsal horns are demarcated by dotted lines. Control animals were also treated at PND4 with TM and are wild-type for murine *Smn* on one allele. $P < 0.001$ when treated mutants were compared with the untreated animals; n = 3 animals in each instance; *t* test. Scale bar – 220μm.



Supplemental Figure 8 – Treated mutants that perished prematurely at ~1 month of age (partial responders) also exhibited lower body weights than mice that survived beyond 6 months of age (full responders); n ≥5 except for partial responders at PND30 where n = 3; $P < 0.05$; *t* test.

Supplemental Figure 9 - Structure of the hybrid donor cassette inserted into the murine *Smn* locus, replace murine exons 7 and 8 and construct the SMN inducible rescue allele. HU – upstream homology region; HD – downstream homology region.