SUPPLEMENTARY FIGURE LEGENDS AND TABLE

Supplementary Fig. 1: Differential regulation of GR isoforms during disease progression in severe SMA mice. **a.** qPCR analysis of *GRβ* mRNA in four different skeletal muscles of post-natal day (P) 2 *Smn*$^{-/-}$*;SMN2* mice compared to WT animals. **b.** qPCR analysis of *GRα* mRNA in four different skeletal muscles of P7 *Smn*$^{-/-}$*;SMN2* mice compared to WT animals. **a-b.** Data represent mean ± SD; n = 3-4 animals per group; two tailed *t-test*; P7 gastro, $p = 0.0415$; ns = not significant.

Supplementary Fig. 2: Expression profiles of *GRα* and *GRβ* do not display a developmental delay pattern. qPCR analysis of *GRα* and *GRβ* mRNAs in four different skeletal muscles (*triceps brachii* (triceps), *gastrocnemius* (gastro), *tibialis anterior* (TA) and *quadriceps femoris* (quad)) of *Smn*$^{-/-}$*;SMN2* mice compared to WT animals at post-natal day (P) 0, 2, 5, 7 and 10. Data represent mean ± SD; n = 3-4 animals per group; one-way ANOVA; *$p<0.05$, **$p<0.01$, ***$p<0.001$, ns = not significant.

Supplementary Fig. 3. Expression profile of *Smn* does not significantly fluctuate in skeletal muscles of WT animals from P0 to P10. qPCR analysis of *Smn* mRNA in four different skeletal muscles (*triceps brachii* (triceps), *gastrocnemius* (gastro), *tibialis anterior* (TA) and *quadriceps femoris* (quad)) of *Smn*$^{-/-}$*;SMN2* mice compared to WT animals at post-natal day (P) 0, 2, 5 and 10. Data represent mean ± SD; n = 3-4 animals per group; one-way ANOVA; *$p<0.05$, **$p<0.01$, ns = not significant.

Supplementary Fig. 4: Immunoblot analysis of KLF15 expression in gastrocnemius samples from SMA patients and age-matched controls. a. Description of protein samples loaded in each lane of the immunoblot gel. **b.** KLF15 immunoblot. **c.** Coomassie stain used for total protein quantification and loading control.

Supplementary Fig. 5: Aberrant expression of *Klf15*, *GRα* and *GRβ* does not appear to be SMN dependent. *Smn*$^{-/-}$*;SMN2* mice received facial vein injections at post-natal day (P) 0 and 2 of a cell-penetrating peptide (Pip6a) conjugated to either an *SMN* enhancing phosphorodiamidate oligomer (PMO) (Pip6a-PMO) or a scrambled control PMO sequence (Pip6a-scrambled). Untreated WT and *Smn*$^{-/-}$*;SMN2* mice were also used as controls. qPCR analysis of (a) Klf15, (b) GRα and (c) GRβ in tibialis anterior of untreated WT, untreated *Smn*$^{-/-}$*;SMN2*, Pip6a-PMO-treated *Smn*$^{-/-}$*;SMN2* and Pip6a-scrambled-treated *Smn*$^{-/-}$*;SMN2* mice. **a-c:** Data represent mean ± SD; n = 3-4 animals per group; one-way ANOVA; *$p<0.05$, **$p<0.01$, ****$p<0.0001$, ns = not significant.

Supplementary Fig. 6: Perturbation of circadian expression of *Klf15* in metabolic tissues and spinal cord in severe SMA mice during disease progression. a. qPCR analysis of diurnal expression of *Klf15* mRNA in white

adipose tissue (WAT), liver, brown adipose tissue (BAT), heart and spinal cord (sc) of post-natal day (P) 2 *Smn*$^{-/-}$*;SMN2* mice compared to healthy controls. **b.** qPCR analysis of diurnal expression of *Klf15* mRNA in WAT, BAT, heart, and sc of P7 *Smn*$^{-/-}$*;SMN2* mice compared to healthy littermates. **a-b.** Data represent mean ± SD; n = 3-4 animals per group; two-way ANOVA; **p*<0.05, ***p*<0.01, ****p*<0.001, *****p*<0.0001.

Supplementary Fig. 7: Dose-dependent effect of prednisolone on weight and survival of severe SMA mice and healthy littermates. a. Weight curves of *Smn*$^{-/-}$*;SMN2* mice treated with different concentrations of prednisolone (2.5 mg/kg, 5 mg/kg and 10 mg/kg) vs untreated animals. Data represent mean ± SD; n = 4-16 animals per group; two-way ANOVA; ****p*<0.001, ns = not significant. **b.** Lifespan of *Smn*$^{-/-}$*;SMN2* mice treated with different concentrations of prednisolone vs untreated animals. Data represent Kaplan-Meier curves; n = 4-16 animals per group; Log-rank (Mantel-Cox) test; *p* = 0.0009 (untreated vs 5 mg/kg); *p* = 0.0008 (untreated vs 10 mg/kg). **c.** Weight curves of healthy control mice treated with different concentrations of prednisolone vs untreated animals. Data represent mean ± SD; n = 10-18 animals per group; two-way ANOVA; **p*<0,05, ***p*<0,01, ****p*<0,001, *****p*<0,0001.

Supplementary Table 1. Amino acid metabolism gene expression changes in muscle from pre- and post-symptomatic severe and intermediate SMA mice.