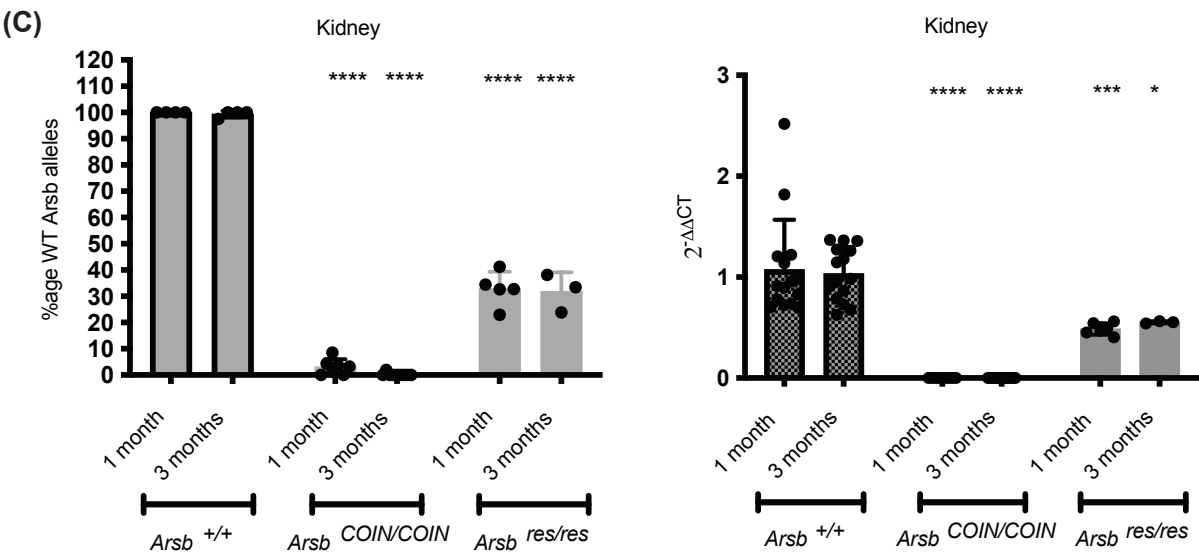
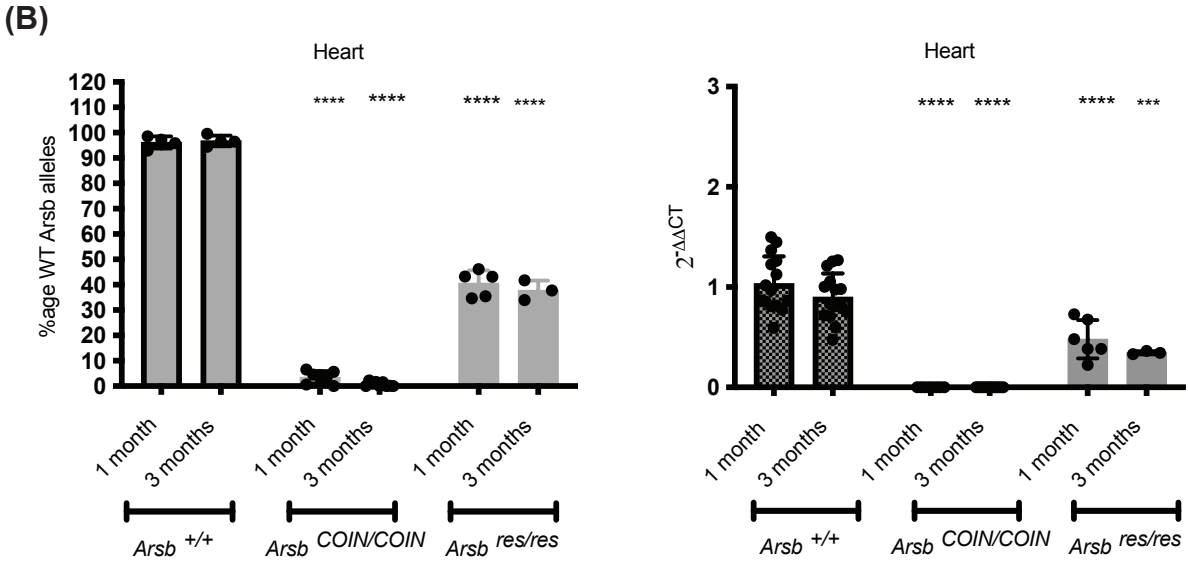
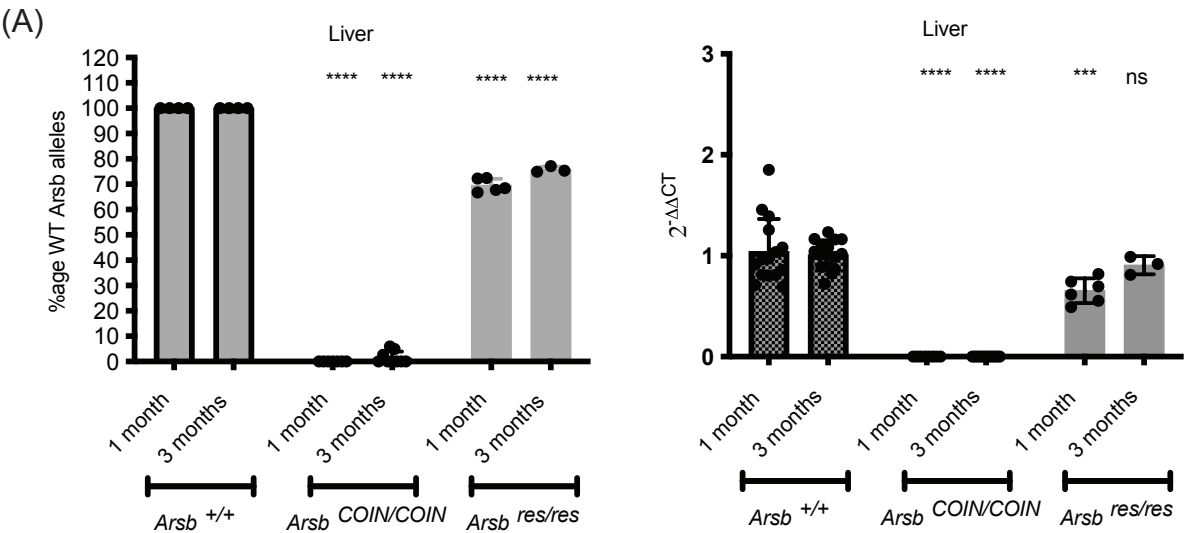
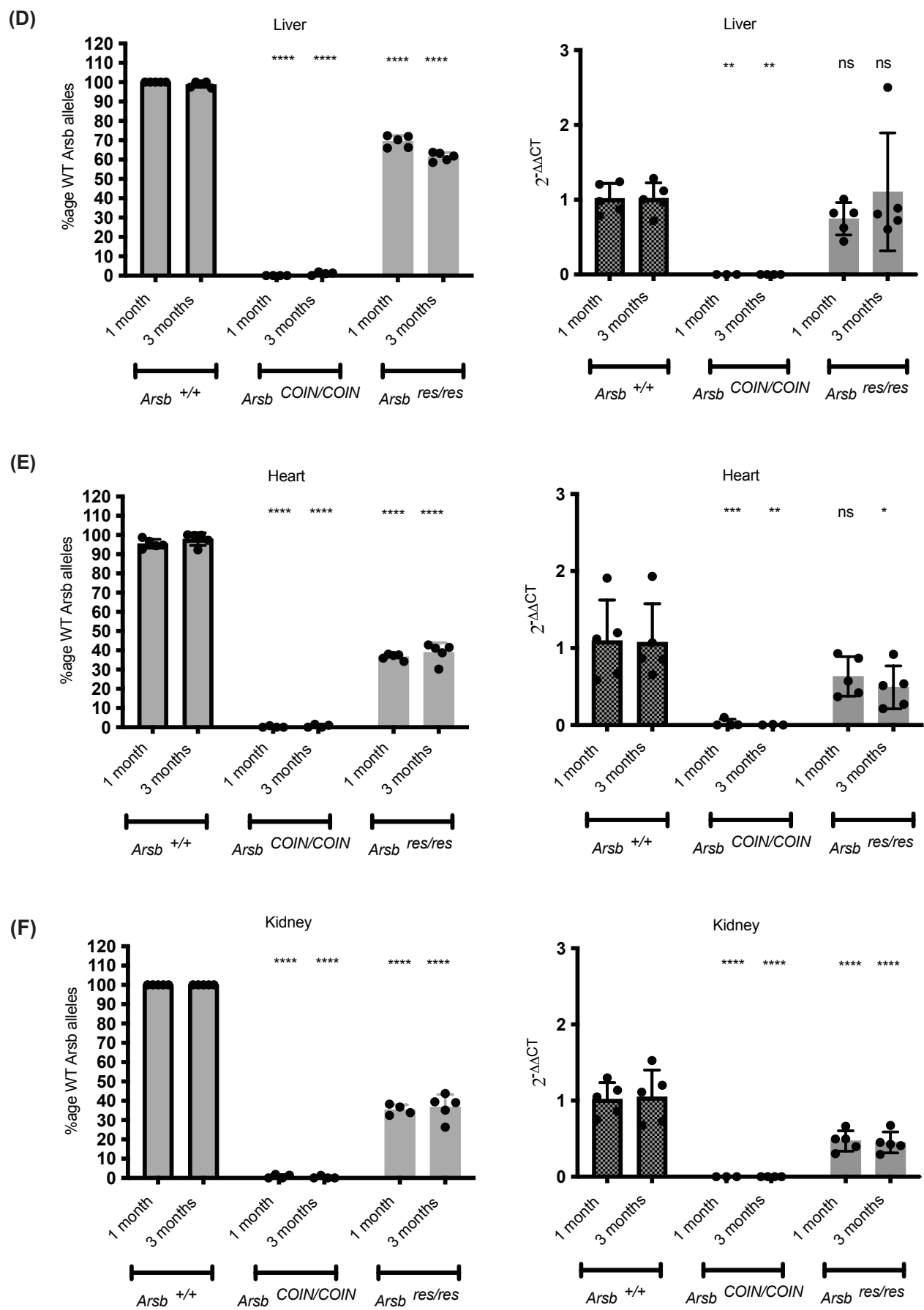




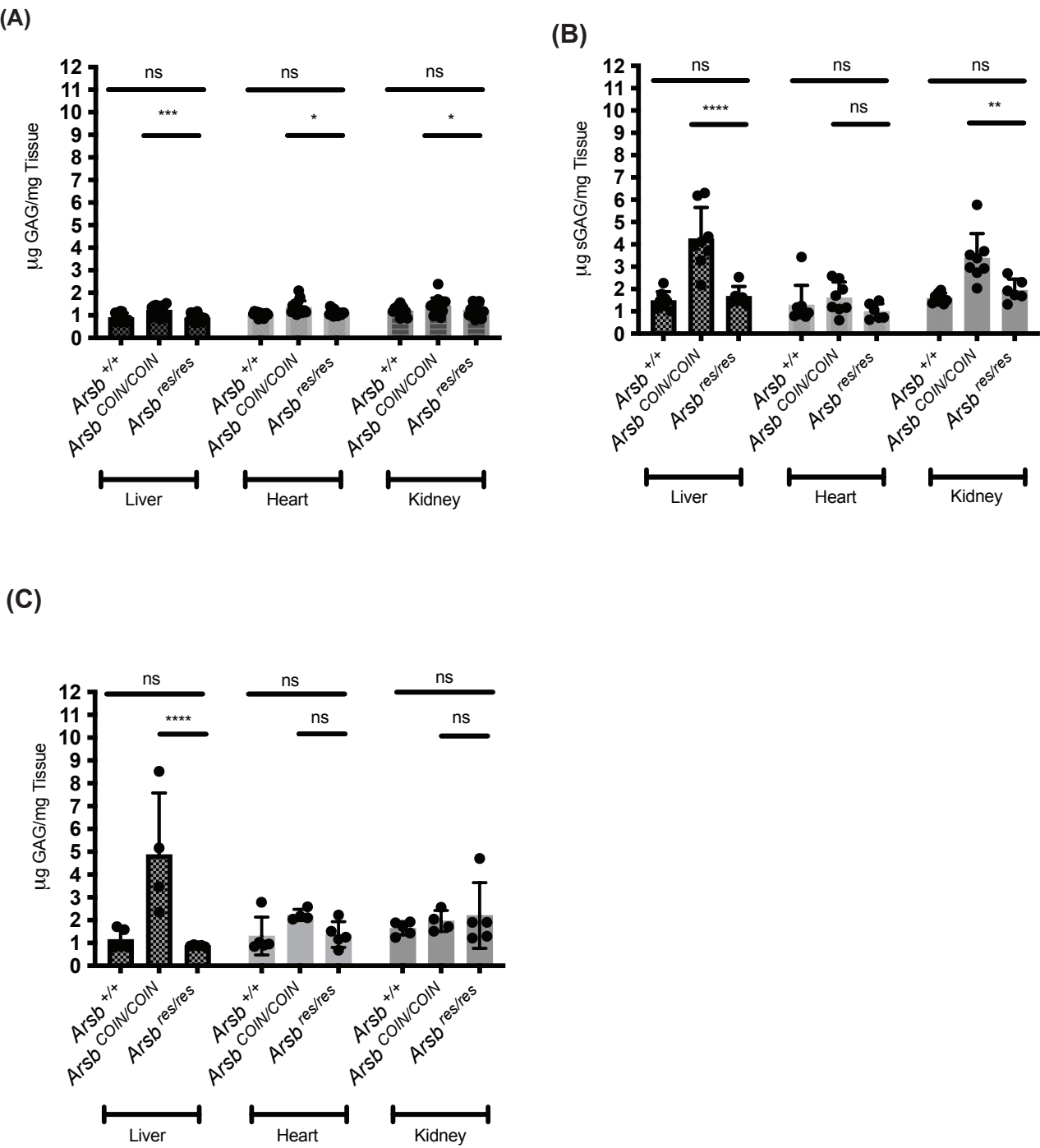
Experimental timeline diagram showing a mouse receiving four consecutive injections (indicated by red arrows) followed by two sacrifice points: "Sacrifice 1 month after 1st Tmx injection" and "Sacrifice 3 months after 1st Tmx injection".

Supplemental Figure 1. Using *Arsb*^{COIN/COIN} mice to model treatment at different timepoints. (A) *Arsb*^{COIN/COIN} allele design (B) Experimental setup. COIN = Conditional Inversion, DSC = drug selection cassette

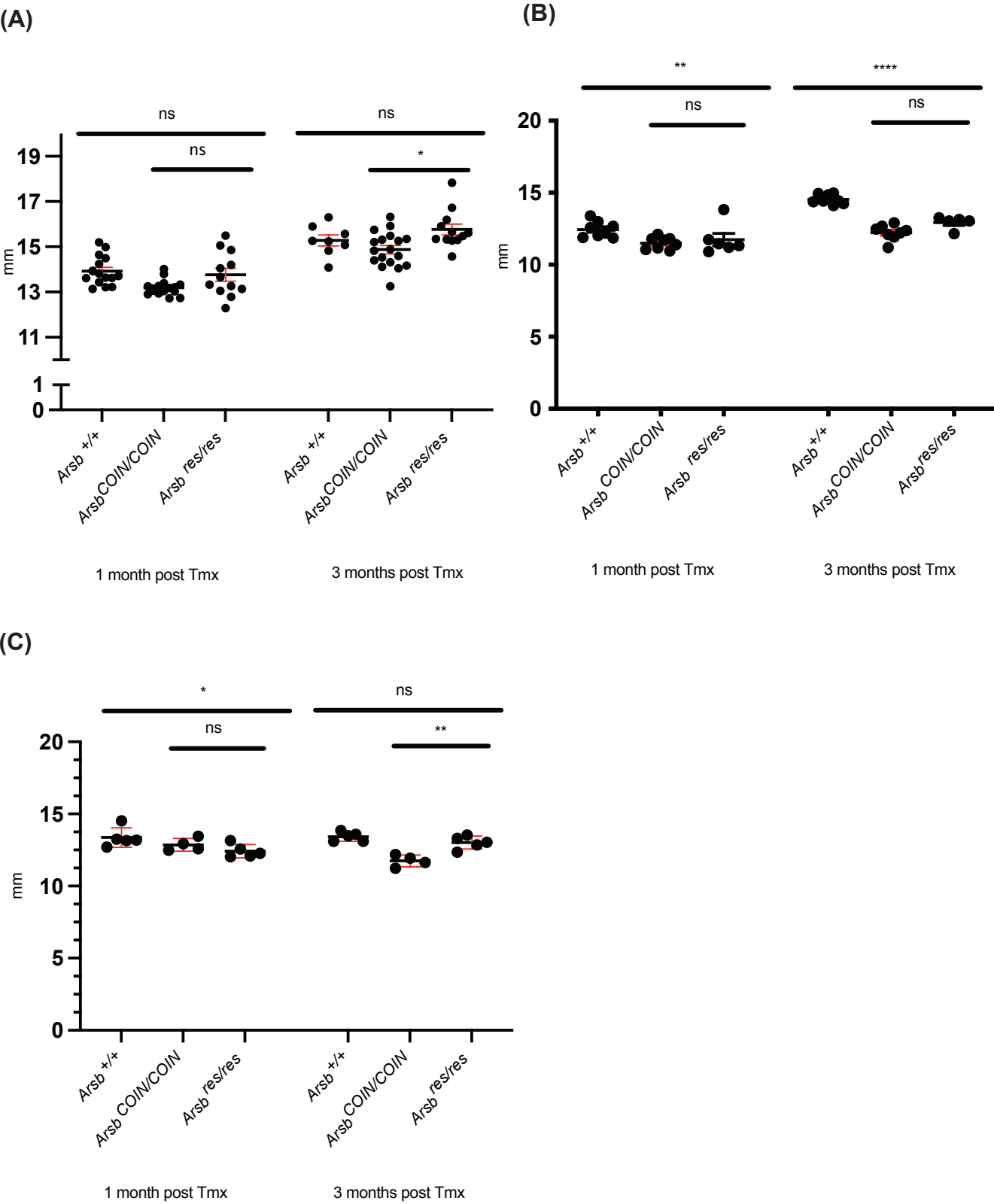




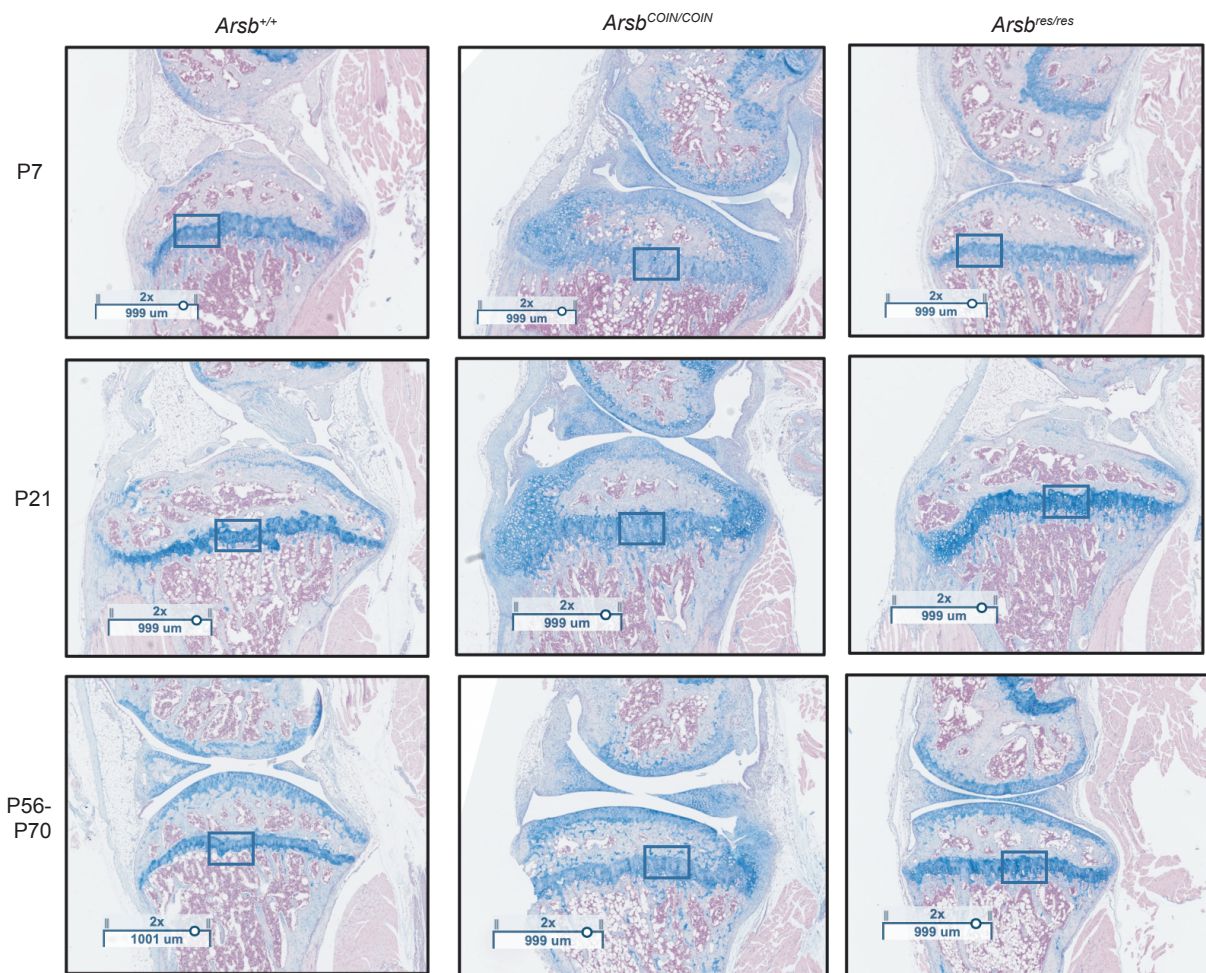
Supplemental Figure 2. *Arsb*^{COIN/COIN} allele recombination rates and transcript abundance in peripheral organs when tamoxifen is delivered at P21 or P56-P70 show recombination occurs with tamoxifen delivery, and corresponds with appearance of transcript. (A) Liver at P21 (B) Heart at P21 (C) Kidney at P21 (D) Liver at P56-P70 (E) Heart at P56-P70 (F) Kidney at P56-P70. Percentage recombination is assessed as ΔCT of *Arsb* Lox71 specific sequence compared to a serial standard, with GAPDH as a reference. Transcript abundance is assessed as $\Delta\Delta\text{CT}$ against Wt samples as references. Data are shown as the mean $\pm$ SD (n=3 to 9). Two-way ANOVAs with Tukey's multiple comparisons were performed, as indicated. * $P<.05$, ** $P<.01$, *** $P<.001$, **** $P<.0001$, ns = not significant



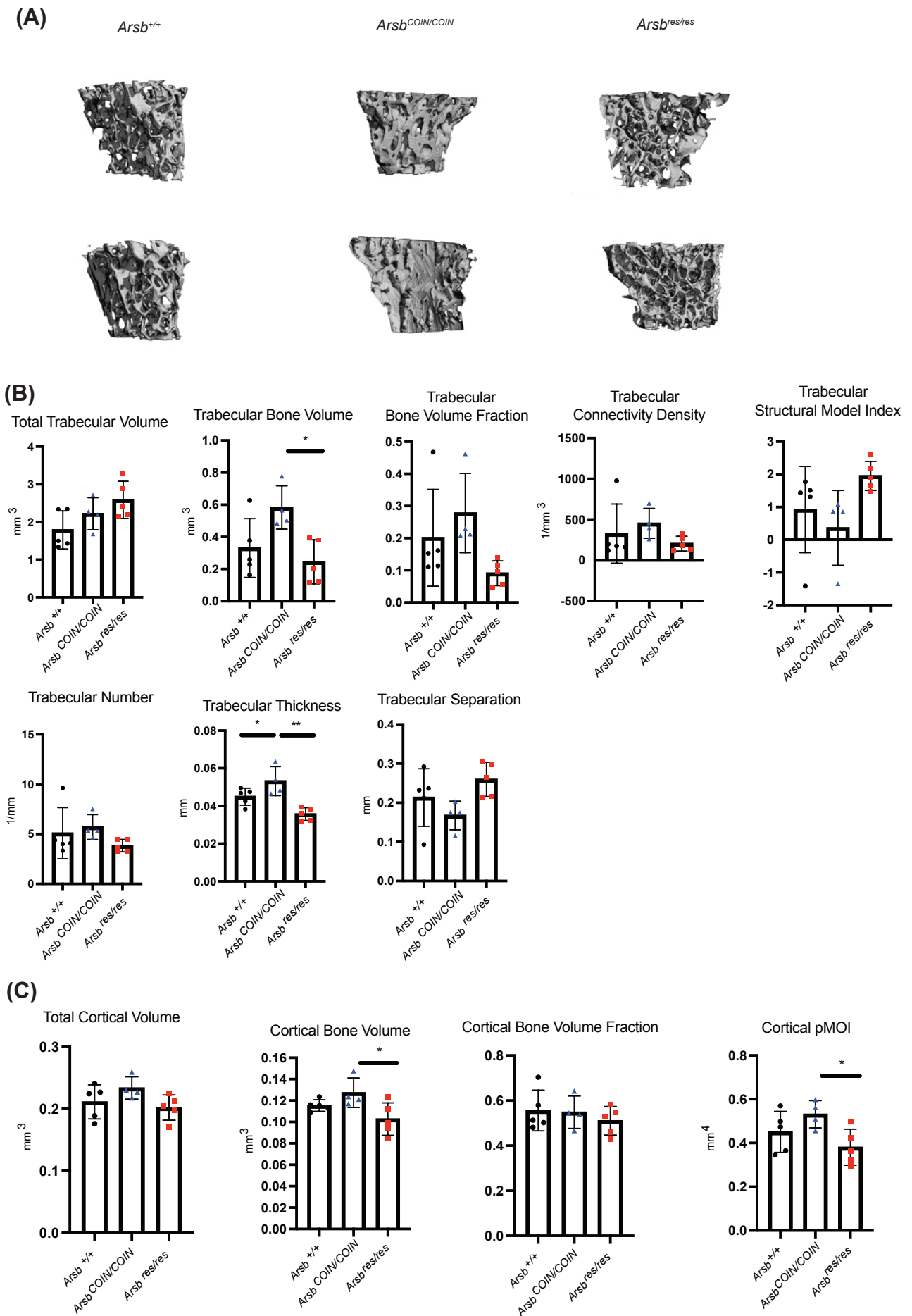
Supplemental Figure 3. Restoration of *Arsb* expression corrects GAG levels to normal in peripheral organs independent of initiation of treatment. (A) 1 month after tamoxifen is delivered at P7; (B) 1 month after tamoxifen is delivered at P21 (C) 1 month after tamoxifen is delivered at P56-P70. Data are shown as the mean $\pm$ SD (n =4 to 16). Two-way ANOVAs with Tukey's multiple comparisons were performed, as indicated. * $P<.05$, ** $P<.01$, *** $P<.001$, **** $P<.0001$, ns = not significant



Supplemental Figure 4. Vertebral Column Lengths show full rescue to WT levels with restoration at P7. L2 to L6 lengths were approximated with (A) tamoxifen delivered at P7; (B) tamoxifen delivered at P21; (C) tamoxifen delivered at P56-P70. Two-way ANOVAs with Tukey's multiple comparisons were performed, as indicated. * $P < .05$, ** $P < .001$, **** $P < .0001$, ns = not significant



Supplemental Figure 6. Restoration of *Arsb* at P7 results in rescue of growth plate defects. Alcian blue stained tibial growth plates from *Arsb*^{+/+}, *Arsb*^{COIN/COIN}, and *Arsb*^{res/res} mice at 3 months post tamoxifen treatment from P7 (top), P21 (middle), and P56-P70 (bottom) mice at 2X magnification. Rectangular boxes indicate regions depicted at 10X in Figure 5A.



Supplemental Figure 7. Restoration of *Arsb* expression at P56-P70 improves femoral bone mass. **(A)** High resolution microCT images of femoral distal metaphyses at 3 months post tamoxifen treatment **(B)** quantification of trabecular readouts **(C)** quantification of cortical readouts. Data are shown as the mean $\pm$ SD ($n=4$ to 5). Repeated measures one-way ANOVAs were performed, as indicated. * $P<.05$, ** $P<.01$, *** $P<.001$, **** $P<.0001$