

Supplemental Figures-Legends

Figure 1 : TN-401 and AAV9:mPkp2 preserved ejection fraction and right ventricle size, reduced arrhythmia scores, and improved lifespan relative to HBSS-treated *Pkp2-cKO* Animals

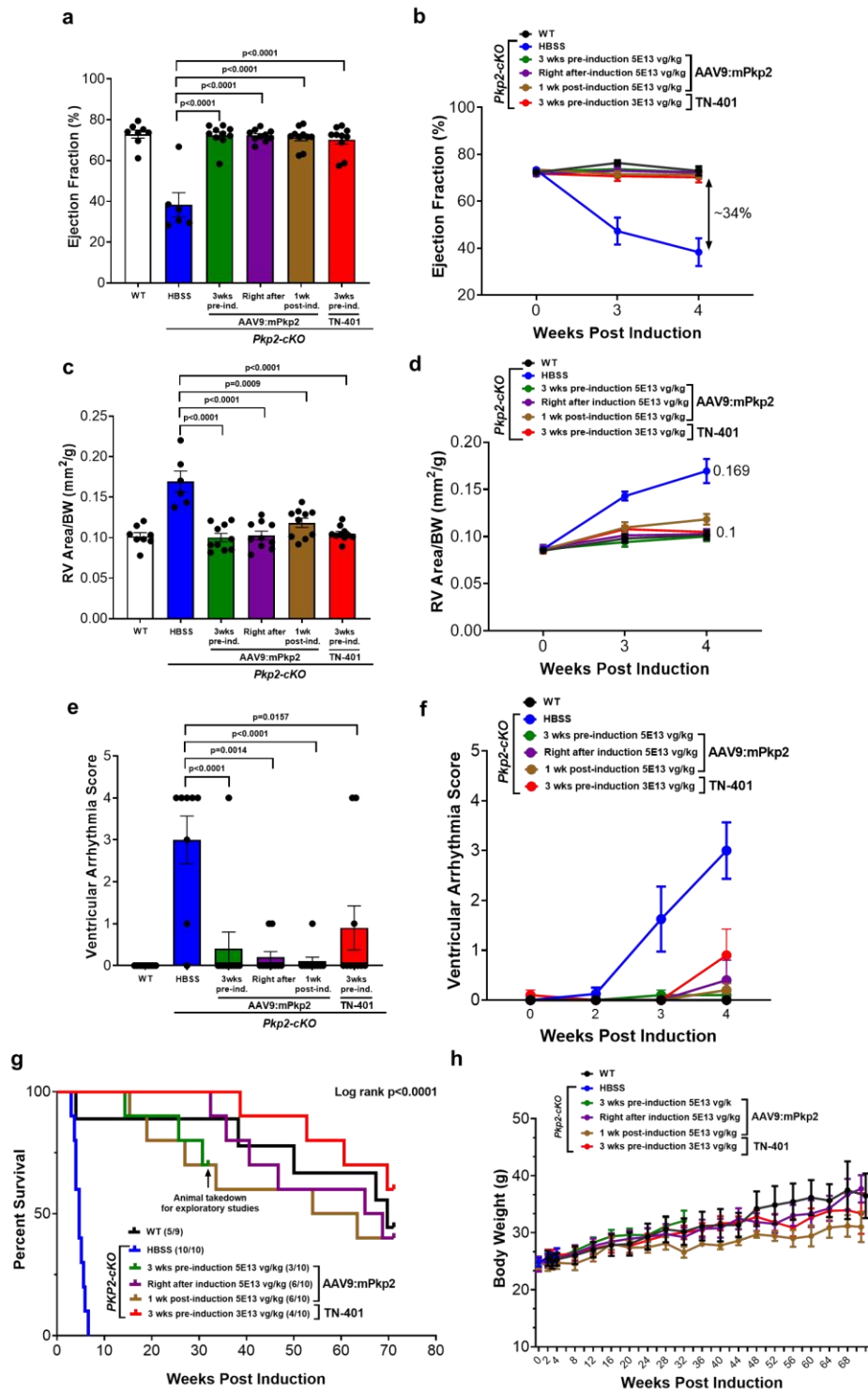


Figure 1. **a)** EF and **b)** EF progression at 4 weeks post-induction. AAV9:mPkp2 treatments at different intervention times and TN-401 treatment significantly prevented decline of EF. RV chamber dilation was measured by RV area normalized to body weight. **c)** RV/BW and **d)** RV/BW progression at 4 weeks post-induction. Animals that were euthanized or died prior to the last echo were excluded from the EF progression and LV Mass graphs. Incidence of ventricular arrhythmia was quantified during 30 minutes of recording of anesthetized animals. The frequency and severity of the spontaneous arrhythmia were recorded and categorized based on the grading chart in suppl. Table 1. **e)** Ventricular arrhythmia score distribution of individual animals at 4 weeks post tamoxifen induction and **f)** ventricular arrhythmia score progression demonstrated that all treatment groups significantly reduced arrhythmia events compared to HBSS-treated *Pkp2-cKO* animals. **g)** Kaplan–Meier survival curve showed that both TN-401 and AAV9:mPkp2 treatment extended life span of *Pkp2-cKO* mice after 72 weeks post induction. *Pkp2-cKO* animals treated 3 weeks before induction with AAV9:mPkp2 were euthanized at 32 weeks for exploratory ex-vivo studies. Numbers in paratheses showed dead vs live animals by the time of takedown. **h)** Animals were weighed weekly from start of induction up to 71 weeks post-induction, at which time the animals were taken down for terminal cardiac assessment. HBSS-treated *Pkp2-cKO* animals reached the humane endpoint by 6 weeks post-induction. There was no concerning decline in body weight for the treatment groups (all animals, including the ones that were found dead or euthanized were included). HBSS served as vehicle control. P-value: Student's t-test. Error bar: s.e.m. (Standard Error of the Mean).

Table 1: Arrhythmia grade chat*

Grade	Arrhythmias
5	S-VT/VF/Cardiac Sudden Death
4	NSVT
3	>100 PVCs, couplets and triplets
2	>50, <100 PVCs
1	<50 PVCs, PJs, AV block
0	<10 PVCs

* The frequency and severity of the spontaneous arrhythmia, including premature ventricular contractions (PVC), premature junctional complexes (PJC), atrioventricular (AV) block, non-sustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (S-VT), ventricular fibrillation (VF) were recorded and evaluated for overall arrhythmia score.