



AFTX-201: A Novel Investigational AAV Gene Therapy for the Treatment of BAG3-Associated Dilated Cardiomyopathy

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Disclosures

- I am an employee of Affinia Therapeutics

Low BAG3 associated with reduced cardiac contractility in Dilated Cardiomyopathy

BAG3 mutation



Functional BAG3 protein

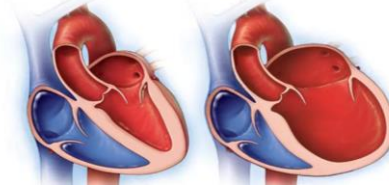


Cardiac contractility



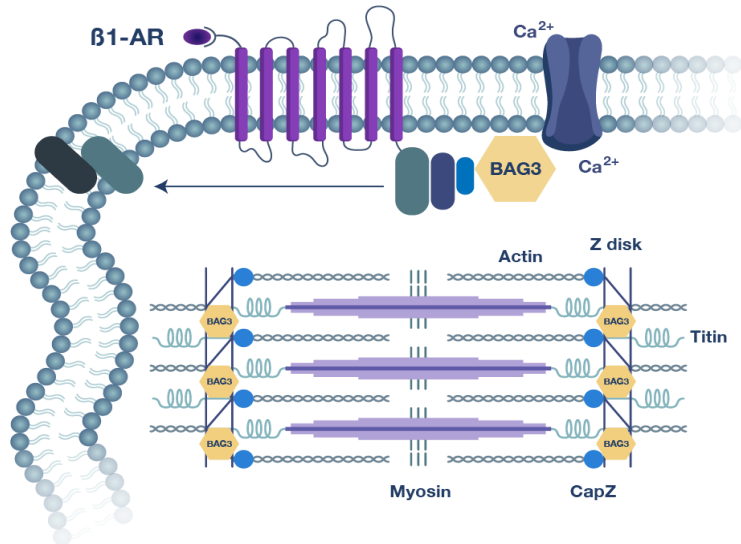
Dilated heart

Patient exercise capacity

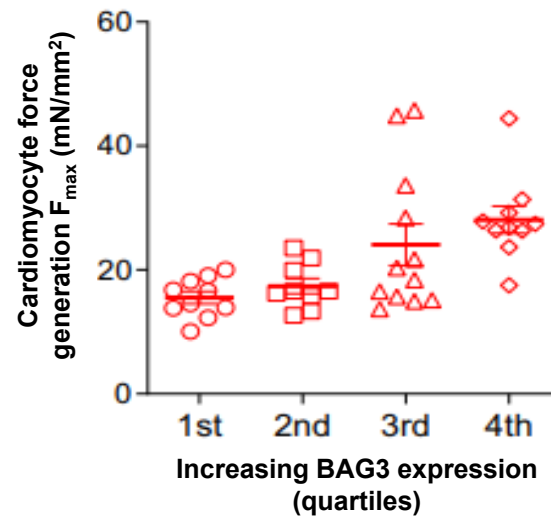


Healthy Dilated

BAG3 plays critical role in protein quality control & sarcomeric integrity



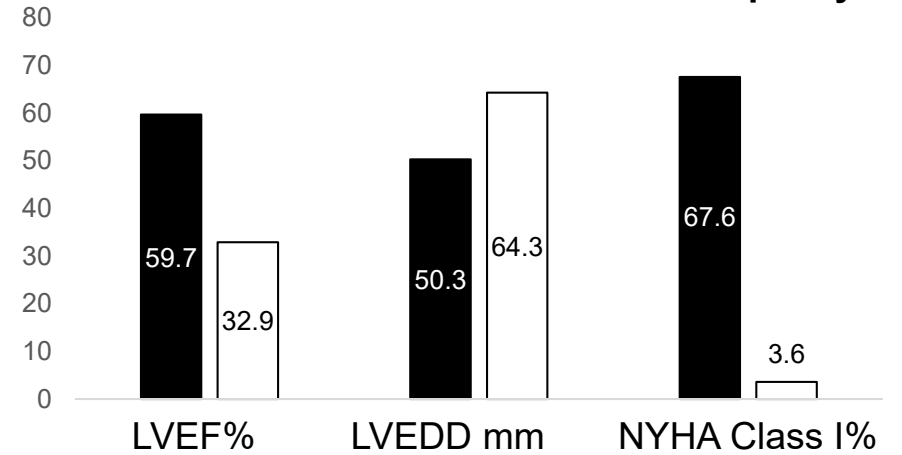
Low BAG3 associated with ↓ Cardiac Contractility



↓ ejection fraction

↑ heart dilation

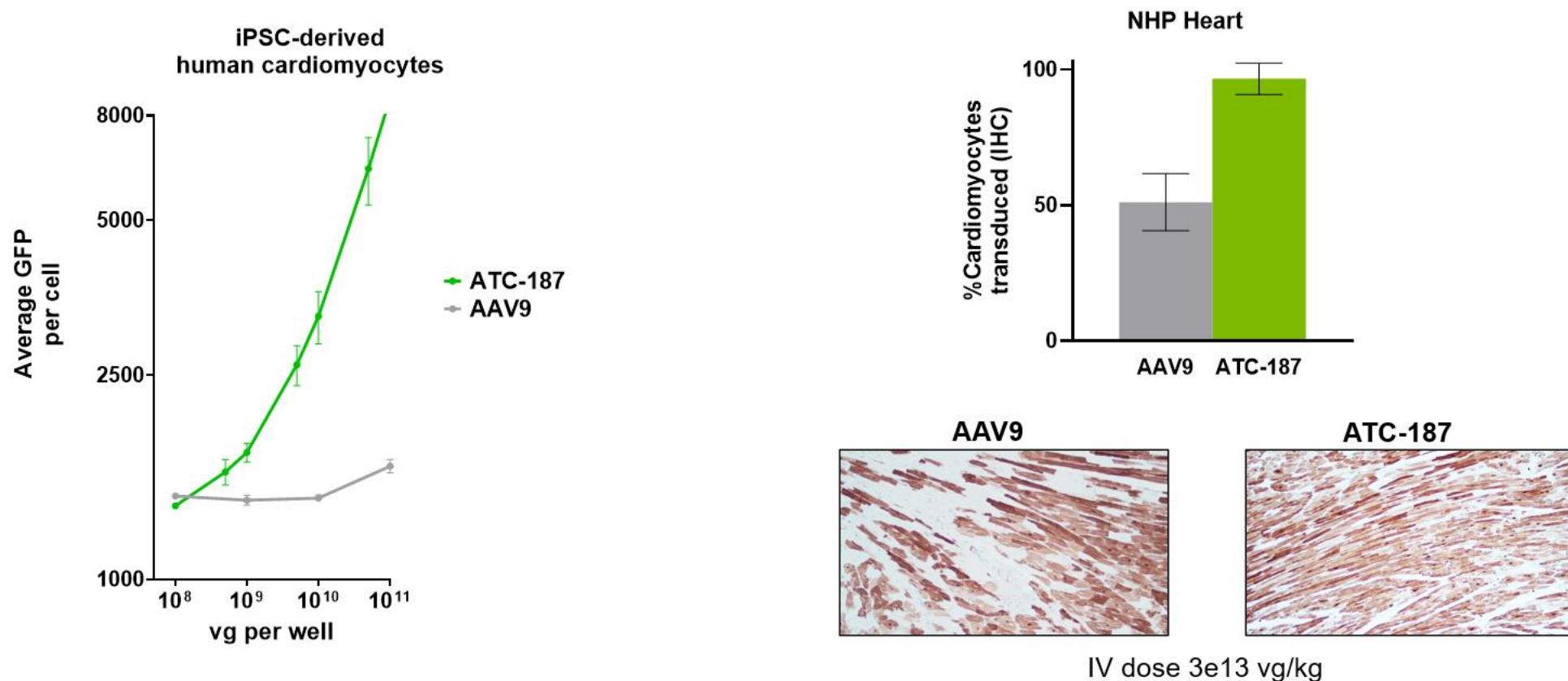
↓ exercise capacity



■ No DCM
□ BAG3 DCM

Engineered ATC-187 capsid was selected for AFTX-201 based on superior cardiomyocyte transduction vs. AAV9

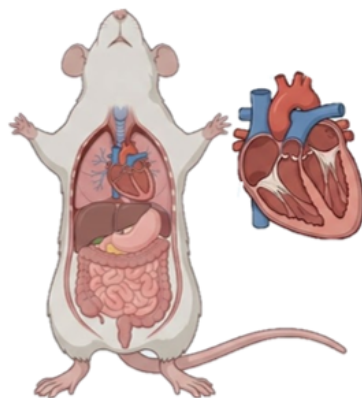
ATC-187 outperforms AAV9 for cardiomyocyte transduction



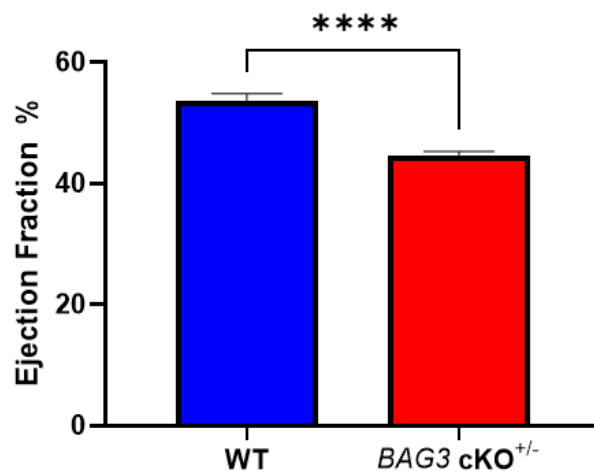
Left: Human iPSC-derived cardiomyocytes 96-well assay; 50K cells per well; 72h incubation; in duplicate
Right: %Cardiomyocytes +ve for GFP in heart left ventricles after IV dose 3e13 vg/kg and 28-day in life in NHPs

BAG3 cKO^{+/-} conditional haploinsufficiency mouse model of Dilated Cardiomyopathy recapitulates human disease

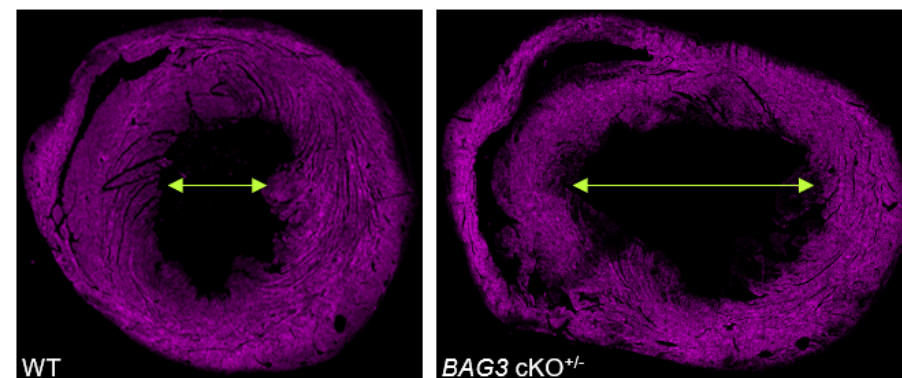
BAG3 cKO^{+/-} mouse



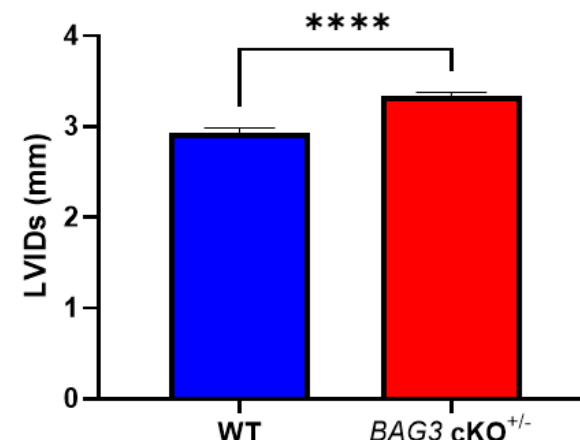
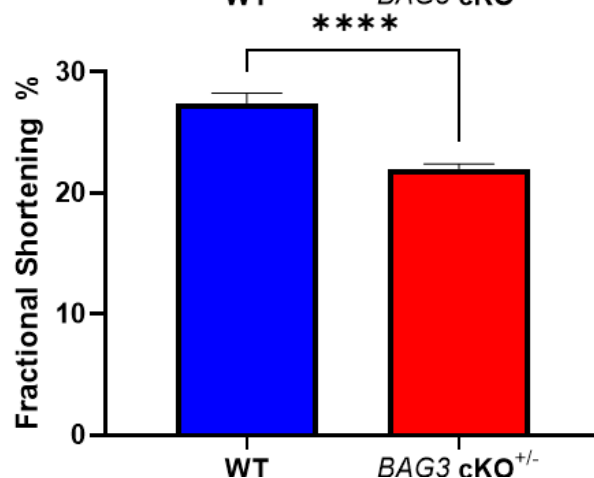
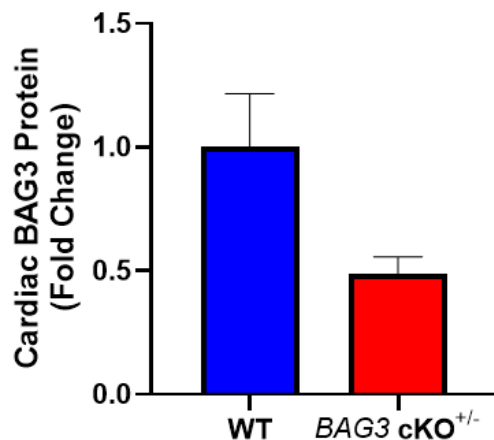
Cardiac functional deficit (contractility)



Cardiac dilation

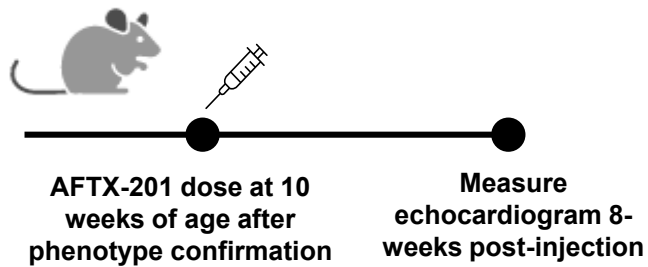


Hearts stained with pan-BAG3 Immunofluorescence (purple)

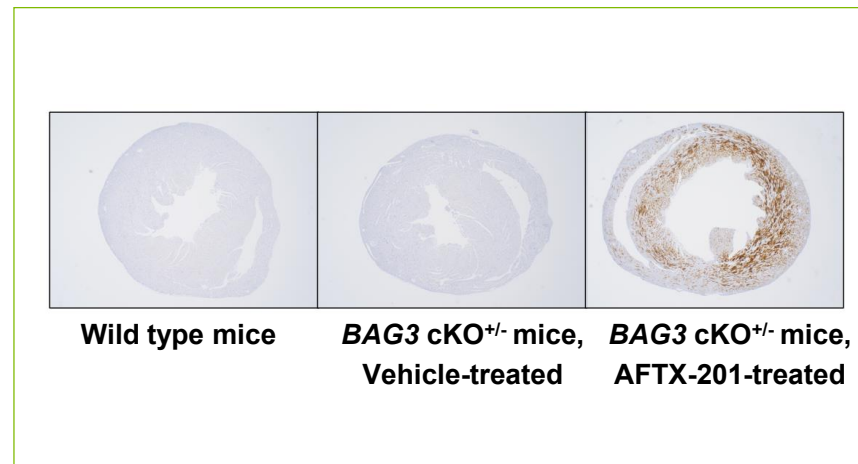


In *BAG3* cKO^{+/-} mice, the AFTX-201 MED of 9e11 vg/kg IV increases cardiac BAG3 protein and normalizes ejection fraction 8 weeks post-dose

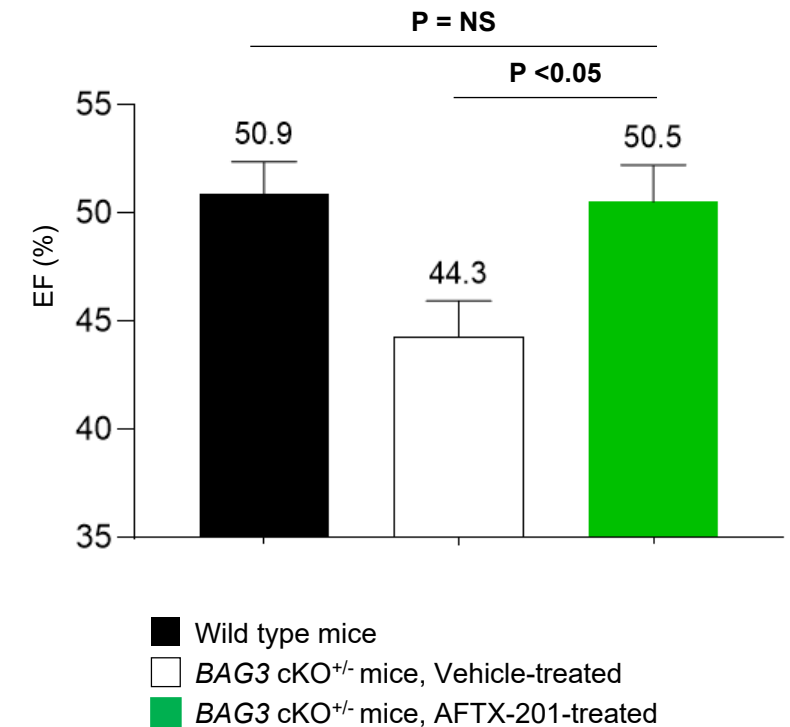
AFTX-201 is dosed post-phenotype confirmation in *BAG3* cKO^{+/-} mice



AFTX-201-derived human BAG3 protein is increased in heart

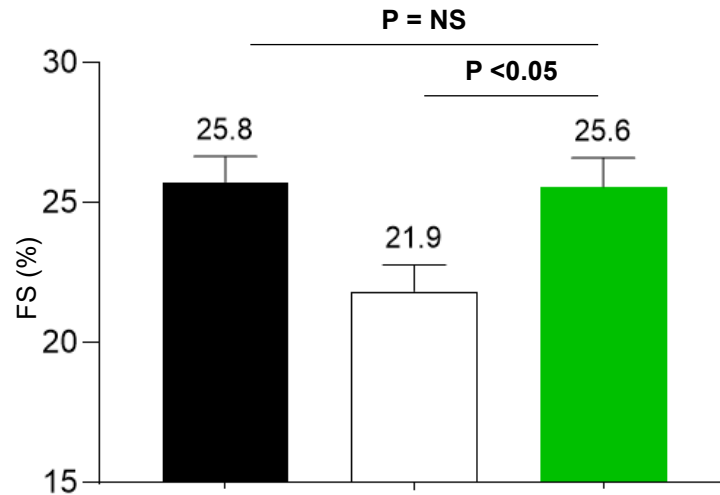


AFTX-201 normalizes ejection fraction to wild type

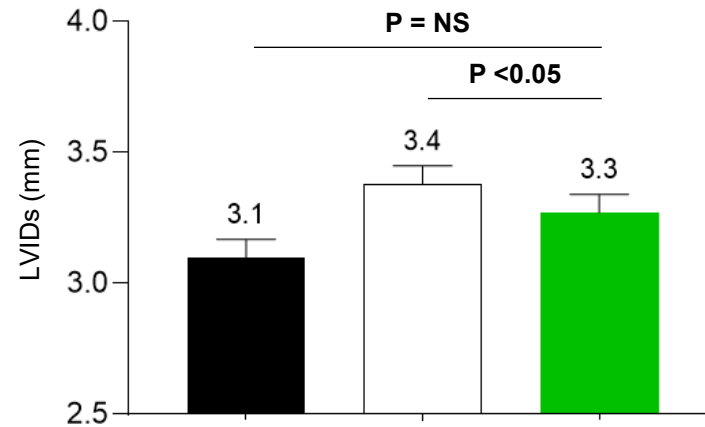


In *BAG3* cKO^{+/-} mice, AFTX-201 also reverses the structural defects of the heart that are hallmark features of the disease

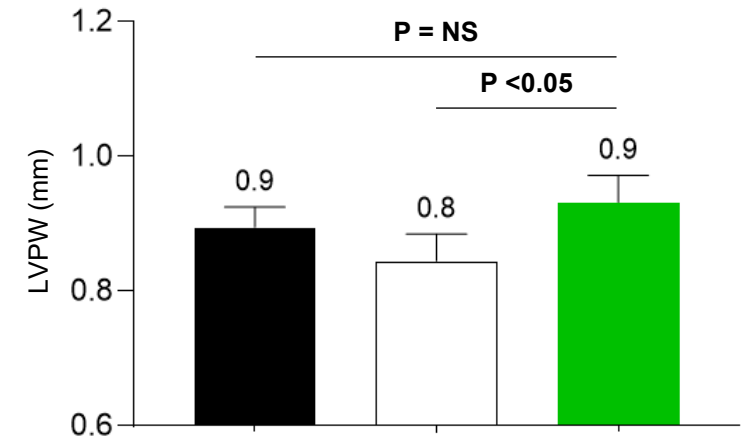
AFTX-201 normalizes Fractional Shortening (FS) to wild type



AFTX-201 normalizes Left Ventricular Internal Diameter, systolic (LVIDs) to wild type



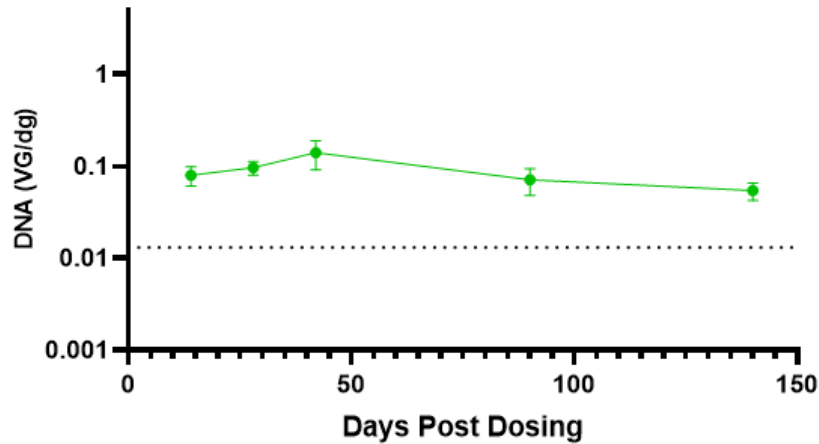
AFTX-201 normalizes Posterior Wall Thickness, systolic (LVPWs) to wild type



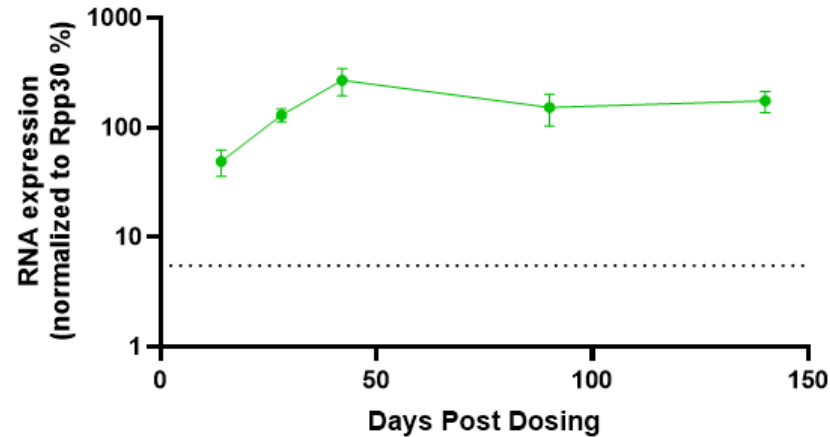
- Wild type mice
- BAG3 cKO^{+/-} mice, Vehicle-treated
- BAG3 cKO^{+/-} mice, AFTX-201-treated

In *BAG3* cKO^{+/-} mice, AFTX-201-derived *BAG3* DNA, RNA, and protein are sustained through the end of the study which is representative of the lifespan of the mice

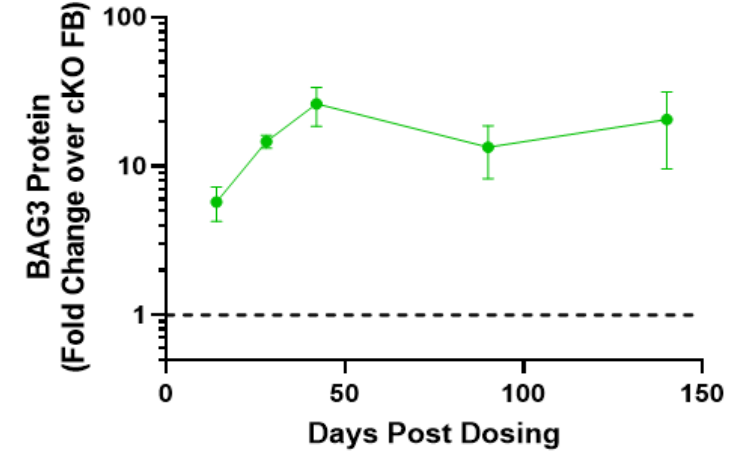
Cardiac *BAG3* DNA (vg/dg) is sustained



Cardiac *BAG3* mRNA (%RPP30) is sustained



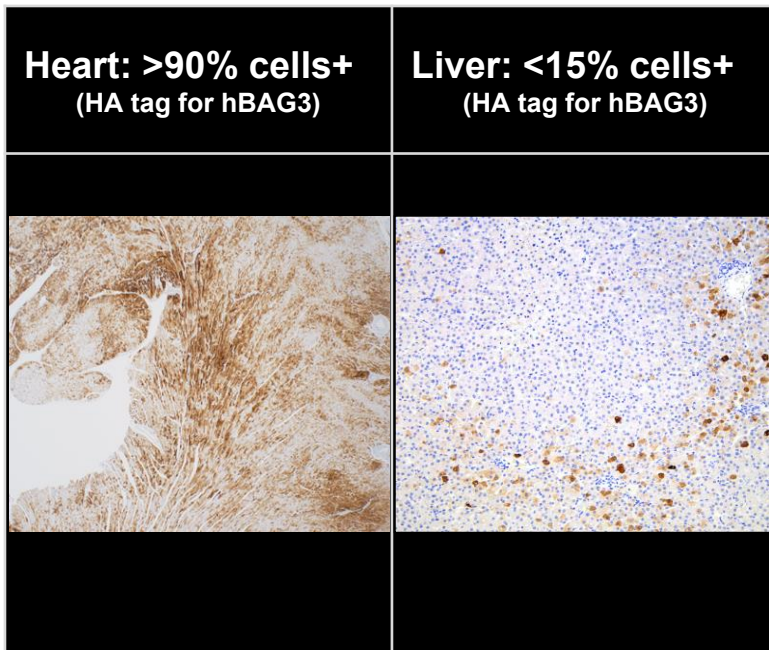
Cardiac *BAG3* protein is sustained



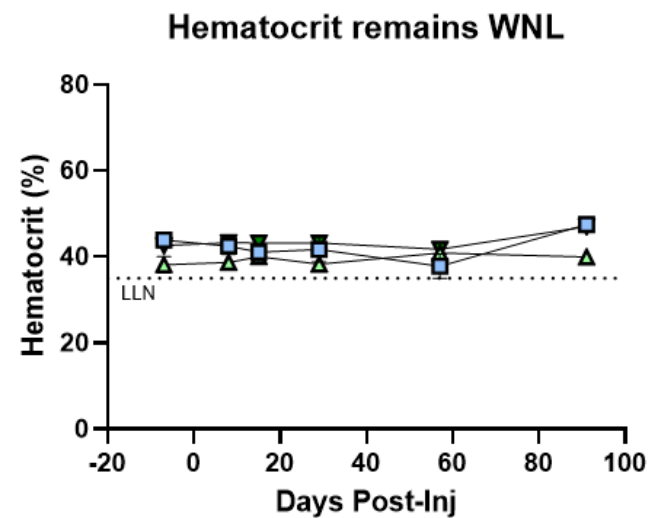
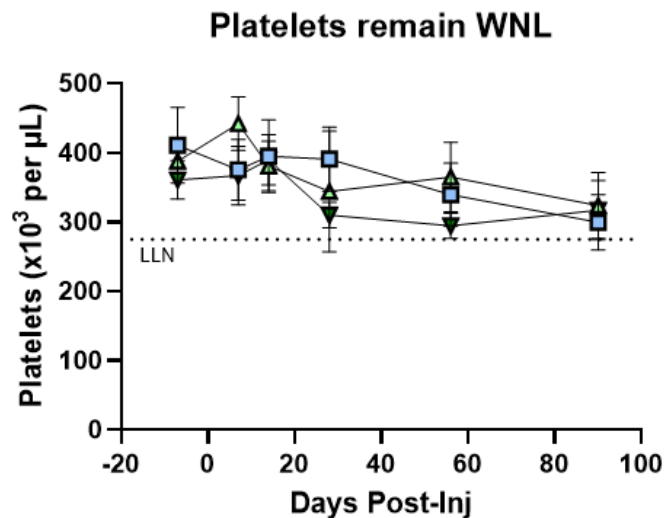
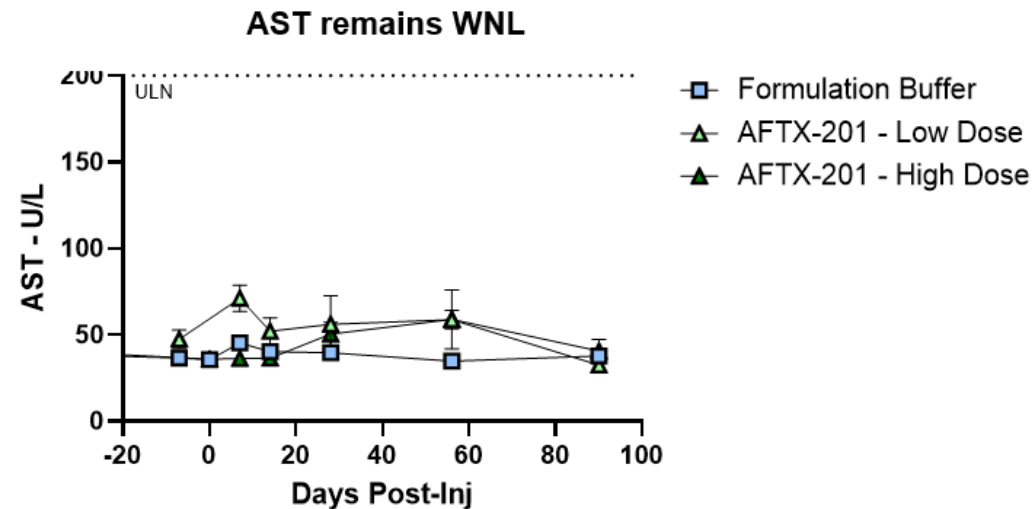
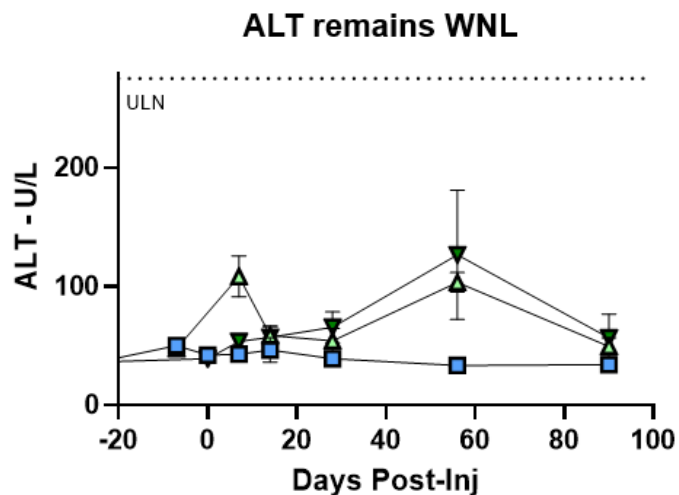
In NHPs, AFTX-201 shows safety advantages in dose-limiting systemic toxicities related to the AAV class

✓ No liver enzyme excursions or complement-mediated toxicity seen

- **Planned doses in the clinic are 5 – 10-fold lower than for conventional capsids**
- **No significant safety findings**
 - No AFTX-201 related mortality or clinical sequelae
 - ALT and AST below upper limit of normal
 - No evidence of complement-mediated toxicity
- **Compelling BAG3 pharmacodynamic measures in heart**
 - % cells+
 - DNA
 - RNA
 - Protein



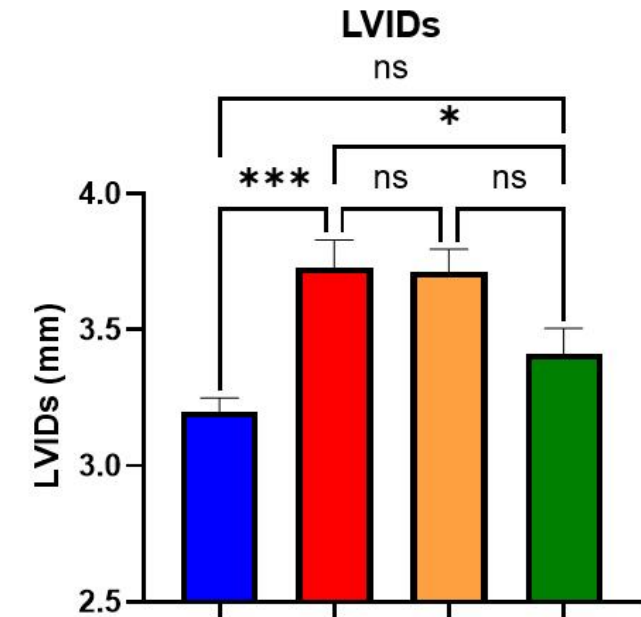
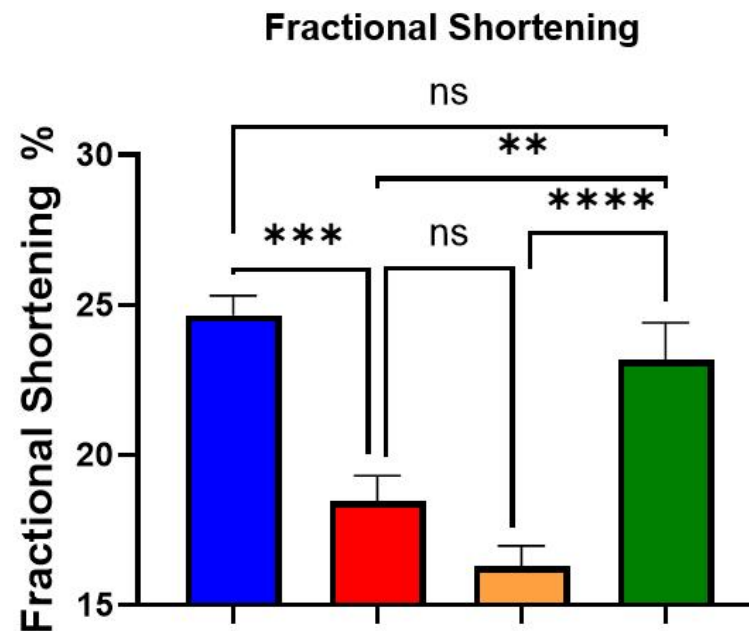
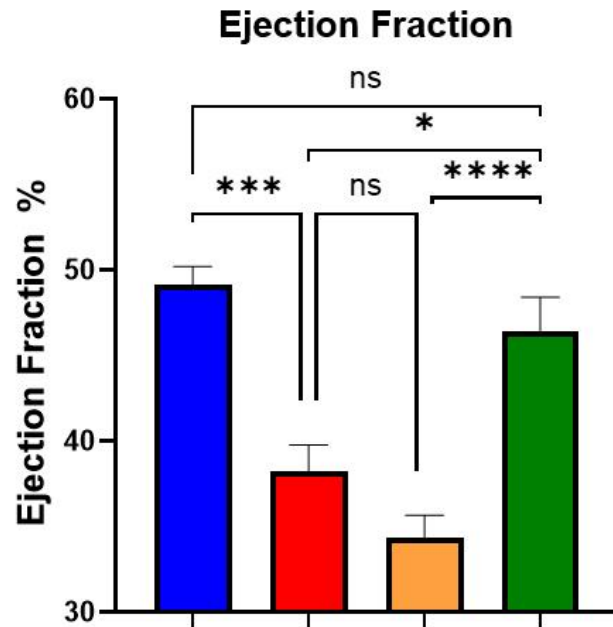
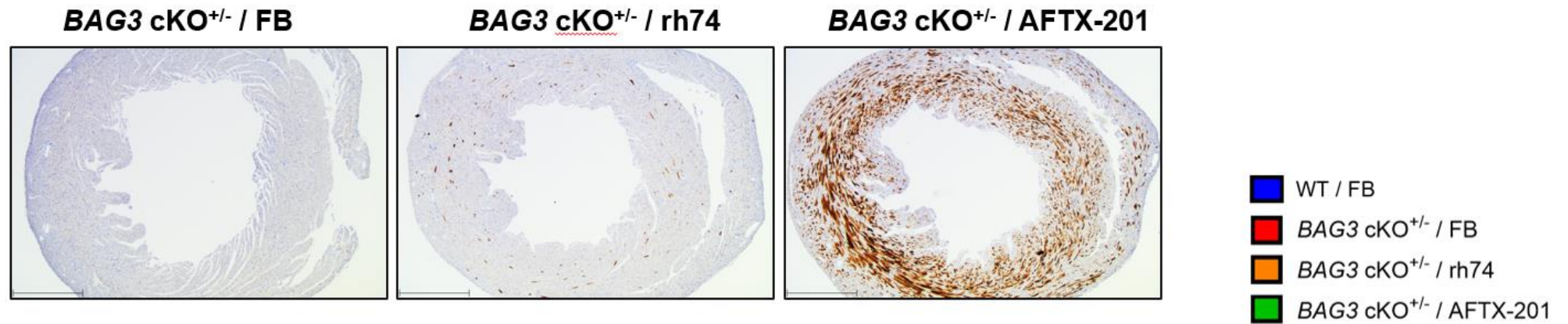
In NHPs, AFTX-201 shows no LFTs excursions, or evidence of complement-mediated toxicity without prophylactic immunosuppressants



AFTX-201 IV dosing in NHPs, n=3 per dose-level, Data shown for 3-month in-life duration

ULN=upper limit; LLN=lower limit; WNL= Within Normal Limits of normal published in Park *et al.* Lab Anim Res 2016: 32(2), 79-86

In a head-to-head study, AFTX-201 was efficacious in *BAG3* cKO^{+/-} mice at 9e11 vg/kg (MED), effect not seen with rh74-based construct



AFTX-201 (HA-tagged) vs rh74 capsid comparison efficacy study in 10 WoA *BAG3* cKO^{+/-}; ****P<0.0001, ***P<0.001, **P<0.01, *P<0.05; MED: Minimum effective dose; similar results of superior therapeutic efficacy were seen in head-to-head study vs AAV9

Phase 1b/2 multicenter, open-label, dose-exploration and dose-expansion trial of AFTX-201 in adults with BAG3–associated DCM (UPBEAT[®] trial)

Background:

- The UPBEAT[®] trial measures myocardial BAG3 restoration and cardiac functional outcomes following a single systemic dose of AFTX-201
- FDA IND and Health Canada CTA approvals have been obtained, multiple sites across US and Canada to support clinical development

Eligibility:

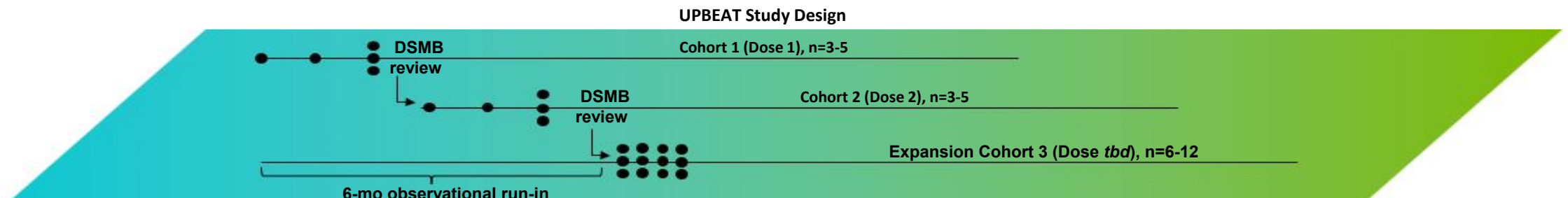
- Male or female, 18-55 years of age with truncating BAG3 mutation, DCM with LVEF <45%, NYHA Class II or III heart failure symptoms

Primary Outcome Measures:

- Safety and tolerability of AFTX-201 over 12 months post dose

Secondary Outcome Measures:

- Assessment of the extent of AFTX-201 transduction, myocardial BAG3 protein expression at baseline, 3 and 12 months
- Cardiovascular function (LVEF, pVO₂) and structure. Clinical features of heart failure including functional classification by NYHA class and quality of life over 12 months
- Safety and tolerability of AFTX-201 over 60 months post dose



AFTX-201: Summary

- ✓ Efficacy: increased BAG3 expression normalized DCM phenotype in *BAG3* cKO^{+/-} disease model
 - Minimum effective dose identified to be 9e11 vg/kg in *BAG3* cKO^{+/-} disease model
- ✓ Differentiation vs conventional capsids
 - Superior efficacy and pharmacodynamics with AFTX-201 (vs dose and cargo matched AAVrh74 and AAV9)
- ✓ Durability: Stable pharmacodynamics in *BAG3* cKO^{+/-} disease model
 - Up to study duration, 140 days, representing the model lifespan
- ✓ Nonhuman primate studies:
 - Dose-dependent increase in biodistribution and expression
 - Safety demonstrated through comprehensive toxicological evaluation in absence of prophylactic immunosuppression
 - No LFT elevation, complement activation or histopathological findings at proposed clinical doses
- ✓ Regulatory filings:
 - IND approved in January 2026, and Health Canada CTA approved March 2026
 - Fast Track Designation by FDA
- UPBEAT© AFTX-201 clinical trial study design: Poster 2363
 - Contact: clinicaltrials@affiniatx.com; NCT07426419

Acknowledgements

Affinia Therapeutics Team

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