Systemic Delivery of Human TNNT2 Gene Therapy Using the Novel Capsid POLARIS-101™ Improves Cardiac Function in the TNNT2 R141W Knock-in Mouse Model of Dilated Cardiomyopathy

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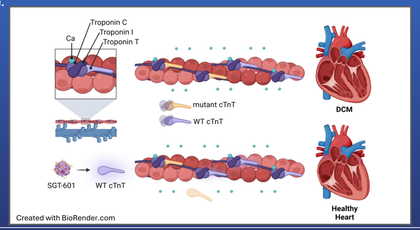
SOLID BIOSCIENCES

INTRODUCTION

Pathogenic variants in the gene encoding cardiac troponin T (cTnT) are associated with an aggressive, early onset form of dilated cardiomyopathy (DCM) which carries significant morbidity and mortality. cTnT is a critical component of the thin filament of the sarcomere that regulates actomyosin interaction and contraction in response to calcium. TNNT2 pathogenic variants causing DCM are usually associated with calcium desensitization and decreased ATPase activity. The *Tnnt2* Arg141Trp (R141W) knock-in (KI) mouse model demonstrates the hallmarks of DCM: it develops left ventricular dilation, depressed myocardial contractility, and exhibits early mortality.

The SGT-601 therapeutic genetic payload developed for this indication contains a cDNA encoding human wild type cTnT driven by a cardiac-specific promoter and is packaged in POLARIS-101™ (formerly known as AAV-SLB101), Solid Biosciences' novel, rationally engineered muscle-tropic capsid. SGT-601 delivers healthy cTnT protein (adult isoform sequenced from adult human heart tissue) which replaces mutant cTnT protein in the sarcomere.



STUDY OVERVIEW

DOSE RESPONSE EFFICACY STUDY IN MOUSE MODEL OF DISEASE

Week -1	Day 1	Weeks 4, 8, 12, 16, 20	6 months
Baseline Echo	IV administration (Dose 1->Dose 5)	Interim Echo Every 4 weeks	Final Echo Tissue Collection

TOXICOLOGY STUDY IN NHPS

Day 1	Days 3-29	Day 92
IV administration (Dose 1-2-> 3.0E14 vg/kg) Baseline labs/biomarkers/Echo/NAb/ELISpot	Serum Clinical Chemistry Cardiac Troponin I/CK-MB/Myoglobin Complement NAb/ELISpot	Serum Clinical Chemistry Cardiac Troponin I/CK-MB/Myoglobin Echo Tissue Collection

To evaluate therapeutic efficacy following restoration of cTnT expression in the mouse myocardium, SGT-601 was systemically delivered in R141W KI mice following onset of the disease process. R141W KI mice were treated with SGT-601 and evaluated longitudinally (echocardiography and survival) for 6 months following treatment. In addition, SGT-601 was evaluated in non-human primates (NHPs) across two studies with 45-day and 3-month post-dose endpoints. At study endpoint, tissues were collected and evaluated for vector genome biodistribution, mRNA and protein expression, mRNA and protein localization, and histopathology.

DOSE RESPONSE IN BIODISTRIBUTION AND EXPRESSION 6 MONTHS POST TREATMENT

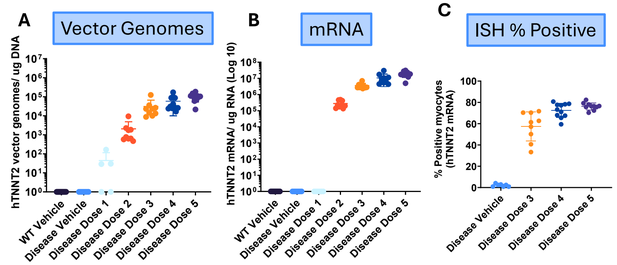


Figure 1: (A) Vector genomes in ventricle tissue collected 6 months post-dose. (B) Human TNNT2 mRNA in ventricle tissue collected 6 months post-dose. (C) ISH analysis quantifying the % positive human TNNT2 cardiomyocytes in ventricle tissue 6 months post-dose. N=10-14 per dose.

DOSE RESPONSE PROTEIN EXPRESSION AND LOCALIZATION 6 MONTHS POST TREATMENT

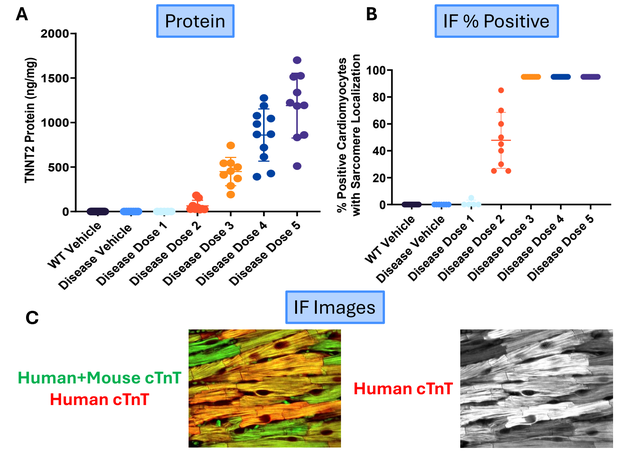


Figure 2: (A) Human transgene protein measured by LC/MS in ventricle tissue collected 6 months post-dose. (B) Immunofluorescence (IF) analysis quantifying the % positive human cTnT cardiomyocytes in ventricle tissue 6 months post-dose. (C) Representative IF images showing proper localization of human cTnT protein to the sarcomere in ventricle tissue. N=10-14 per dose.

CARDIAC FUNCTION IMPROVED ≥ 8 WEEKS POST-SGT-601

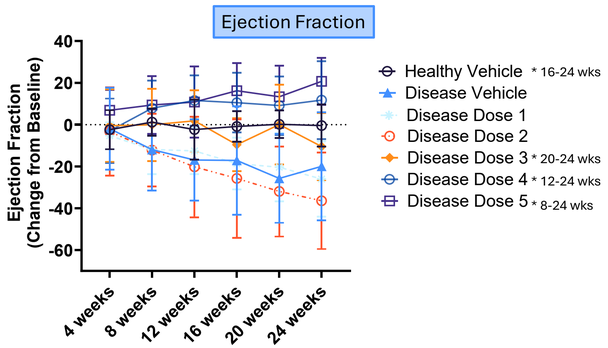


Figure 3: Ejection fraction measurements from echocardiography represented as change from baseline. Disease mice were dosed after the onset of disease and had a 20% reduction in ejection fraction compared to healthy mice. Statistics: linear regression model with Dunnett's test between each group and disease vehicle, *≤0.05.

LEFT VENTRICLE STRUCTURE IMPROVED ≥ 8 WEEKS POST-SGT-601

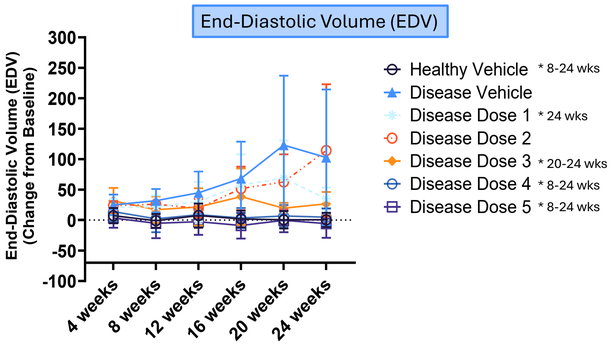


Figure 4: End-diastolic volume measurements from echocardiography represented as change from baseline. Statistics: two-way ANOVA with Dunnett's test between each group and disease vehicle, *≤0.05.

SURVIVAL IMPROVED 6 MONTHS POST-SGT-601

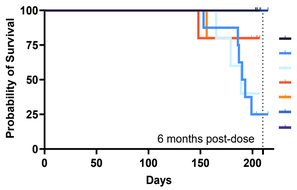


Figure 5: Probability of survival in male animals shown. Statistics: log-rank tests comparing each group and disease vehicle, *≤0.05. All females survived to study endpoint except for one female in dose 1.

# Males Dead/ Total		
Dose (vg/kg)	20 weeks post-dose	24 weeks post-dose
Vehicle	1/8	6/8
Dose 1	1/5	3/5
Dose 2	1/5	1/5
Dose 3	1/5	1/5
Dose 4	0/5	0/5
Dose 5	0/5	0/5

SGT-601 SAFE IN NHPS 3 MONTHS POST-DOSE

- SGT-601 demonstrates a favorable safety and tolerability profile in NHPs, with no adverse cardiac findings and only transient, non-clinically significant laboratory changes at the highest dose
- No SGT-601 related findings in histopathology, hematology, coagulation, cardiac biomarkers, or cardiac function (echocardiography)
- Transient, asymptomatic increases in liver enzymes (AST and ALT) were observed at the highest dose (3.0E14 vg/kg), resolving without associated pathology
- Complement activation (Bb) was observed at the highest dose (3.0E14 vg/kg), without activation of downstream terminal pathway activation (no changes in C3a)
- No detectable T-cell responses to human TNNT2 by ELISpot
- SGT-601 doses animals were NAb positive at Days 29 and 91, consistent with expected humoral responses to AAV.
- Overall, SGT-601 was well-tolerated at all doses, with a no-observed-adverse-effect-level (NOAEL) established at 3.0E14 vg/kg

SUMMARY AND CONCLUSIONS

- SGT-601 delivered durable cardiac expression, functional improvement, and survival benefit in a genetic model of TNNT2 cardiomyopathy with a supportive nonclinical safety profile
- SGT-601 drove robust, dose dependent cardiac expression of TNNT2 (vector genomes, mRNA, and protein) with appropriate cardiomyocyte localization up to 6 months post-dose
- SGT-601 improved cardiac function and structure in a dose-dependent manner from 8 weeks through 6 months post-dose
- SGT-601 extended survival in male disease mice at 6 months post-dose
- SGT-601 was well tolerated in NHPs with a no-observed-adverse-effect-level (NOAEL) at the highest dose tested (3.0E14 vg/kg) 3 months post-dose
- Collectively, these data demonstrate that a single systemic administration of SGT-601 provides durable functional rescue and survival benefit, supporting its advancement as a gene therapy for TNNT2-mediated cardiomyopathy

Presented at American Society of Gene & Cell Therapy, May 5-11, 2026, Boston, Ma