A Novel AAV Gene Therapy Strategy to Correct Calcium Dysregulation in Catecholaminergic Polymorphic Ventricular Tachycardia

Meghan Soustek-Kramer[1], Justin DeFrancisco[1], Jamie Marshall[1], Alessandro Trancuccio[2], Deni Kukavica[2], Andrea Mazzanti[2], Carlo Napolitano[2], Silvia G Priori[2], Stephanie Stoddard[1], Afshin Farzaneh-Far[1], Gabriel Brooks[1], Jessie Hanrahan[1], Nicolas Christoforou[1]

[1]Solid Biosciences Inc., Charlestown, MA, USA, [2]ICS Maugeri, Pavia, Italy

INTRODUCTION

Background: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but severe cardiac disorder, often triggered by physical or emotional stress, and is associated with mutations in the ryanodine receptor 2 (*RYR2*) gene. Patients with CPVT face significant risks, including syncope, cardiac arrest, and sudden death. Despite available treatments, many individuals remain susceptible to dangerous arrhythmic events, highlighting the urgent need for innovative therapeutic strategies. This research explores the potential of adeno-associated virus (AAV)-mediated gene therapy to augment expression of calsequestrin 2 (CASQ2) within the sarcoplasmic reticulum of cardiomyocytes. By increasing CASQ2, the therapy aims to improve calcium buffering and stabilize RYR2 channels, thereby preventing abnormal calcium leakage during diastole. The goal is to restore normal cardiac rhythm and reduce arrhythmia risk in individuals with CPVT-causing RYR2 mutations.

Methods: A gene therapy candidate, SGT-501, was engineered using an AAV8 vector to deliver the human CASQ2 gene. Its efficacy was assessed in RYR2 mutant mice ($RYR2^{R4496C/+}$) three months following a single intravenous delivery at increasing dose levels. Long-term safety and tissue distribution were further evaluated in non-human primates (NHPs) at three and six months post-treatment.

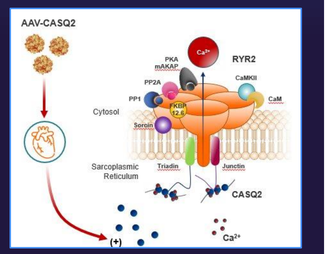
Building on preclinical success, the ARTEMIS Phase 1b trial is designed to investigate the safety, tolerability, and preliminary efficacy of a single intravenous dose of SGT-501 in patients with pathogenic or likely pathogenic RYR2 mutations associated with CPVT. The primary endpoint is the occurrence of treatment-related adverse events, while secondary measures include changes in Ventricular Arrhythmia Score (VAS) during exercise. The study is expected to enroll two adult cohorts before expanding to pediatric participants, following an open-label, multicenter format.

Results: In $RYR2^{R4496C/+}$ mice, SGT-501 administration led to a clear dose-dependent increase in CASQ2 expression at both the mRNA and protein levels. Upon beta-adrenergic stimulation (2mg/kg epinephrine and 120mg/kg caffeine), a significant decrease in ventricular tachycardia (VT) incidence was observed at the mid dose (4/25, 16%) and high dose (1/28, 4%) compared to vehicle (13/25, 52%), with cardiac CASQ2 protein levels measured at 1.6-fold and 6-fold above vehicle levels, respectively. In NHPs, SGT-501 was well tolerated at all doses, with CASQ2 expression confined to cardiac tissue and no adverse effects on cardiac biomarkers or function.

Conclusion: A single dose of SGT-501 effectively rescued electrophysiological abnormalities in a CPVT mouse model and was well-tolerated at all doses in NHPs. These encouraging results provide the foundation for the ARTEMIS Phase 1b clinical trial, which will further evaluate the therapy in patients with CPVT.

MECHANISM OF ACTION

- **CPVT variants** increase the open probability of RYR2 channels, making them prone to spontaneous diastolic Ca^{2+} release
- **β-adrenergic stimulation** further exacerbates Ca^{2+} leak, leading to activation of the Na^+/Ca^{2+} exchanger (NCX) and generation of delayed afterdepolarizations (DADs)
- **DADs** ultimately trigger premature ventricular arrhythmias, which escalate into polymorphic or bidirectional VT
- **SGT-501 (AAV-CASQ2)** is a novel AAV8-based gene therapy that delivers a full-length hCASQ2 transgene under the control of the desmin promoter
- **Augmentation of CASQ2** aims to prolong the RYR2 recovery from refractoriness by:
  - Desensitizing RYR2 through its interactions with the RyR2 complex
  - Acting as a molecular Ca+ buffer to lower free luminal Ca2+ and prolong SR refilling

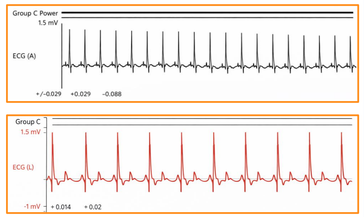


SGT-501 EFFICACY IN A MOUSE MODEL OF CPVT

Mouse Model of CPVT

Genetic Alteration: The R4496C variant involves a single amino acid substitution in *RYR2*. This variant was discovered in CPVT patients.

Rationale for the Model: Mice carrying *RYR2* R4496C exhibit many of the hallmark features of CPVT seen in humans: stress-induced arrhythmias, propensity for bidirectional VT, and diastolic Ca^{2+} leak (Cerrone M, et al. *Circ Res.* 2005;96(10):e77-e82)



Study Schematic

Groups	Strain	Test Article	Dose Level (vg/kg)
1	WT	Vehicle	0
2	$RYR2^{R4496C +/-}$		0
3		AAV-CASQ2	Low
4			Mid
5			High

SGT-501 dose-responsiveness was observed in all tissues with preferential expression in the heart

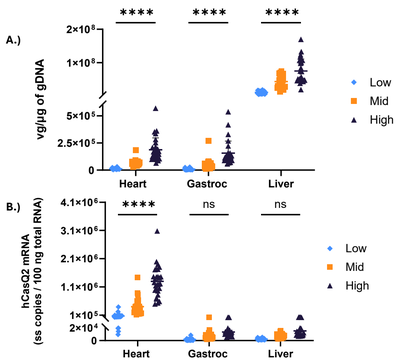


Figure 1. A.) Biodistribution of AAV-CASQ2 in heart, skeletal muscle and liver from $RYR2^{R4496C+/-}$ treated mice (Low, Mid, High dose) 3 months post-dosing. B.) Human CASQ2 transgene expression in heart, skeletal muscle and liver from $RYR2^{R4496C+/-}$ treated mice (Low, Mid, High dose) 3 months post-dosing. Two-way ANOVA with Tukey's multiple comparisons was conducted, *p<0.0005.

SGT-501 EFFICACY IN A MOUSE MODEL OF CPVT

SGT-501 expresses hCASQ2 and diminishes sustained VT in $RYR2^{R4496C+/-}$ mice in a dose-dependent manner

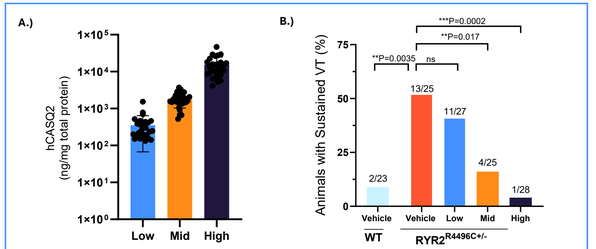


Figure 2. A.) Human specific CASQ2 protein expression in $RYR2^{R4496C+/-}$ AAV-CASQ2 treated mice (Low, Mid, High dose) 3 months post-dosing measured by LC-MS. A 1.1x, 1.6x, or 6x fold increase in hCASQ2 protein levels was observed over endogenous baseline levels with the Low, Mid, and High dose respectively. **B.)** Quantification of the incidence of sustained (>10 seconds) bidirectional ventricular tachycardia (VT) determined by in vivo ECG recordings in WT, $RYR2^{R4496C+/-}$ vehicle, and $RYR2^{R4496C+/-}$ AAV-CASQ2 treated mice (Low, Mid, High dose) 3 months post-dosing following beta-adrenergic challenge (2mg/kg epinephrine and 120mg/kg caffeine). Chi-square statistical analysis is shown along with # of animals presenting with VT out of the total n/group.

SGT-501 SAFETY IN NONHUMAN PRIMATES

SGT-501 was well-tolerated in NHPs within the tested dose range through 6-Months

Dose Levels	Baseline	In Life Readouts	Terminal Timepoints
• Vehicle (N=3/ timepoint) • Low (N=4; 3-mth only) • Mid (N=4 / timepoint) • High (N=4 / timepoint)	• Serum Clinical Chemistry • Jacketed external telemetry • Echocardiography • Respiratory	• Serum Clinical Chemistry • Jacketed external telemetry • Respiratory	• 3- & 6-months • Serum Clinical Chemistry • Jacketed external telemetry • Echocardiography • Tissue Collection & Analysis

Clinical Pathology
- There were no SGT-501 related clinical observations recorded on study.
- There were no SGT-501 related adverse effects associated with hematology or serum clinical chemistry

Histopathology
- There were no macroscopic/microscopic H&E findings noted, no heart fibrosis (Trichome). The liver, spinal cord, and DRGs all had a 'clean' histopathological read.

Echocardiography and JET 3-mo
- Echo was assessed pre-dose and 3- and 6-months post-dose for all animals.
- Jacketed external telemetry assessed (JET) pre-dose, then post-dose every month for 22 consecutive hours per interval.
- There were no SGT-501 related changes identified in JET, and echocardiography evaluation.

No observed adverse effect level (NOAEL): High Dose

ARTEMIS CLINICAL TRIAL: SGT-501 PHASE 1B STUDY

First-in-Human, Open-Label, Multi-Center Study

OBJECTIVE

Primary Objective
- To evaluate the safety and tolerability of a single IV infusion of SGT-501 gene therapy in participants with CPVT

Secondary Objectives
- To evaluate the efficacy of SGT-501 by:
  - Assessing arrhythmia burden during exercise
  - Assessing arrhythmia burden over time

DESIGN

Design

Study includes up to **3 cohorts** based on age and on dose level
- Cohort 1: Participants ≥ 18, Dose Level 1
- Cohort 2[b]: Participants ≥ 18, Dose Level 2[b]
- Cohort 3: Participants ≥ 7 to < 18 years of age, dosed level at or below dose(s) assessed in adults[b]

All participants must have a history of life-threatening ventricular arrhythmic event with documented prior history of a VAS score of ≥ 2, and must be on a stable dose of background beta-blocker and/or flecainide

ENDPOINTS

Primary Endpoint

Incidence of TEAEs through Day 360

Secondary Endpoints

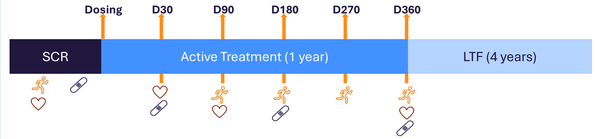
Change from baseline of VAS on exercise treadmill test at Day 180

Exploratory Endpoints

Change from baseline in the incidence of ventricular arrhythmia at Day 180 with ECG patch

DSMB=data and safety monitoring board.
[a]Optional for dose exploration. [b]Based on DSMB recommendation

ARTEMIS Study Design



- Exercise Stress Test
- Echocardiogram
- ECG Patch

SCR: Screening; D: Day; ILR: Implantable Loop Receptor; ICD: Implantable Cardioverter-defibrillator; LTF: Long Term Follow-Up

CONCLUSIONS

- CPVT is a rare inherited channelopathy characterized by stress-induced VT
- Unmet need persists for mechanism-directed durable treatments
- SGT-501 is a 1st in class gene therapy for the treatment of CPVT

- A single administration of SGT-501 was effective in rescuing electrophysiological abnormalities in a RYR2 mouse model of CPVT

- SGT-501 was well tolerated with no adverse observations within the tested dose range through 6-months in NHPs

- The Artemis Study is a first in-human clinical trial evaluating the safety, tolerability and preliminary efficacy of a single IV dose of SGT-501 in participants with CPVT harboring a pathogenic or likely pathogenic RYR2 variant.
  - Trial is now open and enrolling across multiple sites in North America

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