Cardiovascular Clinical Trialist Forum: Cardiac Gene Treatment

An Industry Prospective: Drive to Inflection Point

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Forward Looking Statement

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding future expectations, plans and prospects for the company; the ability to successfully achieve and execute on the company’s goals, priorities and achieve key clinical milestones; the company’s SGT-003, SGT-212, and SGT-501 programs, including expectations for additional CTA filings, site activations, expanded clinical development, production of additional SGT-003, SGT-212, and SGT-501 GMP batches, initiation and enrollment in clinical trials, dosing, and availability of clinical trial data; the company’s expectations submit additional INDs for SGT-501 by the end of 2026; and other statements containing the words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “would,” “working” and similar expressions. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with the company’s ability to advance SGT-003, SGT-212, and SGT-501 , and other programs and platform technologies on the timelines expected or at all; obtain and maintain necessary and desirable approvals from the FDA and other regulatory authorities; replicate in clinical trials positive results found in preclinical studies and early-stage clinical trials of the company’s product candidates; obtain, maintain or protect intellectual property rights related to its product candidates; compete successfully with other companies that are seeking to develop Duchenne, Friedrich’s ataxia, and other neuromuscular and cardiac treatments and gene therapies; manage expenses; and raise the substantial additional capital needed, on the timeline necessary, to continue development of SGT-003, SGT-212, and SGT-501 and other candidates, achieve its other business objectives and continue as a going concern. For a discussion of other risks and uncertainties, and other important factors, any of which could cause the company’s actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties and other important factors, in the company’s most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the company’s views as of the date hereof and should not be relied upon as representing the company’s views as of any date subsequent to the date hereof. The company anticipates that subsequent events and developments will cause the company's views to change. However, while the company may elect to update these forward-looking statements at some point in the future, the company specifically disclaims any obligation to do so.

This presentation contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Acknowledgments

CVCT and Overcome

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CPVT Community

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Solid Biosciences

- Preclinical and clinical development departments

ICS Maugeri

- The Silvia Priori Lab

CPVT=catecholaminergic polymorphic ventricular tachycardia; CVCT=Cardiovascular Clinical Trialist; HiRO=Hearts in Research Organization; ICS=Istituti Clinici Scientifici; SADS=Sudden Arrhythmia Death Syndromes.

Implications of Advanced Therapies for Drug Development Feasibility

Balancing “Time and Resources” vs “Probability of Clinical Success”

Time and Resources

- High CoGS
- Delivery complexity
- Off target safety considerations
- Unknown pharmacodynamics

Probability of Clinical Success

- Clinical development efficiency
- Biologic target engagement
  - Precision targeting

CoGS=cost of goods sold.

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Clinical Development Efficiency

Early infection point

Early signal detection

Lowest number of patients to demonstrate safety and efficacy

Fastest time to meaningful clinical benefit

Meaningful Clinical Benefit: Challenges With Rare Disease

Meaningful clinical benefit = something that affects feel, function, and survival

Optimizing signal detection with feel, function, and survival requires:

Large treatment signal

Frequent events and/or large patient population

Or both

Optimizing Feel, Function, and Survival Detection

Large Treatment Effect

- Rapidly progressive neuromuscular diseases
  - SMA: onasemnogene abeparvovec-xioi (Zolgensma)
- Aggressive oncologic diseases
  - r/r B-cell ALL: tisagenlecleucel (Kymriah)

Large Available Patient Population

- CHF (PARADIGM-HF – sacubitril and valsartan (Entresto)
- ASCVD (VESALIUS-CV – Evolocumab)
- AFib (ARISTOTLE – Apixaban)

AFib=atrial fibrillation; ALL=acute lymphoblastic leukemia; ASCVD=atherosclerotic cardiovascular disease; CHF=congestive heart failure; r/r=relapsed or refractory; SMA=spinal muscular atrophy.

Optimizing Feel, Function, and Survival Detection

Large Treatment Effect

- Rapidly progressive neuromuscular diseases
  - SMA: onasemnogene abeparvovec-xioi (Zolgensma)
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Requiring miraculous treatment effects – too high a bar

Large Available Patient Population

- CHF (PARADIGM-HF – sacubitril and valsartan (Entresto)
- ASCVD (VESALIUS-CV – Evolocumab)
- AFib (ARISTOTLE – Apixaban)

Requiring huge population – challenging in orphan disease

AFib=atrial fibrillation; ALL=acute lymphoblastic leukemia; ASCVD=atherosclerotic cardiovascular disease; CHF=congestive heart failure; r/r=relapsed or refractory; SMA=spinal muscular atrophy.

Accelerated Approval Pathway

In 2012, the US Congress passed the Food and Drug Administration Safety Innovations Act (FDASIA)

Section 901 of FDASIA allows the FDA to base accelerated approval of drugs for serious conditions that fill an unmet medical need on whether the drug affects a surrogate or an intermediate clinical endpoint

A surrogate endpoint is generally a biomarker (eg, laboratory measurement, radiographic image, physical sign) that is thought to predict clinical benefit but is not itself a measure of clinical benefit

- Validated surrogate – known to predict clinical benefit (full approval)
- Reasonably likely surrogate – suggested to predict clinical benefit (accelerated approval)

An intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on IMM and may support accelerated approval when it is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit

IMM=irreversible morbidity and mortality.

FDA. Updated August 21, 2025. Accessed November 12, 2025. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

Main Gene Therapy Trials for Cardiovascular Diseases

Arrhythmogenic Cardiomyopathy

Outcome Measure Categories

Arrhythmia | Imaging | Clinical | PRO | Tissue | Exercise | Hospitalization | Lab

LX2020 for *PKP2*-Mediated Arrhythmogenic Cardiomyopathy (Phase I/II)

RP-A601 for *PKP2*-Mediated Arrhythmogenic Cardiomyopathy (Phase I)

TN-401 for *PKP2*-Mediated Arrhythmogenic Cardiomyopathy (RIDGE-1) (Phase I)

PRO=patient-reported outcome.

Main Gene Therapy Trials for Cardiovascular Diseases
Dilated Cardiomyopathy (DCM)

Outcome Measure Categories

Arrhythmia | Imaging | Clinical | PRO | Tissue | Exercise | Hospitalization | Lab

SGT-003 for Duchenne (Phase I/II)	SGT-003 for Duchenne (Phase III)	RP-A701 for *BAG3*-Dilated Cardiomyopathy (Phase I)	RGX-202 for Duchenne (Phase I/II/III)	GNT0004 for Duchenne (Phase I/II/III)	AAV1/SERCA2a for Duchenne (Phase I/II)	Myocardial Telomere Recapping Study for Dilated Cardiomyopathy (MERCURY-DCM) (Phase I)
Tissue, Exercise	Imaging, Exercise	Arrhythmia, PRO, Tissue, Exercise	Tissue, Exercise	Tissue, Exercise	Imaging, Exercise	Imaging, PRO, Exercise, Lab

AAV=adeno-associated virus.

Main Gene Therapy Trials for Cardiovascular Diseases

Hypertrophic Cardiomyopathy

Outcome Measure Categories

Arrhythmia | Imaging | Clinical | PRO | Tissue | Exercise | Hospitalization | Lab

SGT-212 for Friedreich's Ataxia (Phase I)	ST-920 for Fabry Disease (STAAR) (Phase I/II)	RP-A501 for Danon Disease (Phase II)	AAVrh.10hFXN for Friedreich's Ataxia (Phase I)	rAAV1-CMV-GAA for Pompe Disease (Phase I/II)	GC301 for Pompe Disease (Phase I/II)	AAV2/8-LSPhGAA for Pompe Disease (Phase I)	EXG110 for Fabry Disease (Phase I/II)	TN-201 for Symptomatic MYBPC3 Mutation-Associated HCM (MyPEAK-1) (Phase I/II)
Clinical, Hospitalization, Lab	Imaging, PRO, Tissue	Imaging, PRO, Tissue	Imaging, PRO, Tissue	Exercise	Exercise, PRO	Exercise, Tissue	Imaging, Lab	Imaging, PRO, Tissue

CMV=cytomegalovirus; GAA=acid alpha-glucosidase; HCM=hypertrophic cardiomyopathy.

Main Gene Therapy Trials for Cardiovascular Diseases
Inherited Arrhythmia Syndrome

Outcome Measure Categories

Arrhythmia | Imaging | Clinical | PRO | Tissue | Exercise | Hospitalization | Lab

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SGT-501 for CPVT (ARTEMIS Trial) (Phase I)

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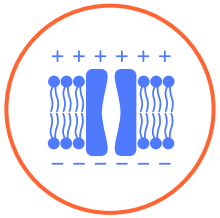
CPVT Represents a High Unmet Need With No Approved Therapies That Treat Underlying Cause of Disease



CPVT is a channelopathy; a genetic mutation affects specific ion channels in cardiomyocytes[1]

Mutations in the genes coding for RYR2 (calcium channel) and CASQ2 (calcium-binding protein) are the most common causes of CPVT[2-4]

Altered calcium ion channels impact electrical conduction and cardiac contraction, and can lead to fatal arrhythmia[2,5-7]

Standard CPVT treatments are used off-label, require strict compliance, and have challenging side effects that are life limiting[8-13]

- Beta blockers
- Flecainide
- Implantable cardioverter defibrillators (ICDs)
- Left cardiac sympathetic denervation

CASQ2=calsequestrine-2; RYR2=ryanodine receptor 2.

1. Abbas M, et al. *Arrhythm Electrophysiol Rev.* 2022;11:e20. 2. Wleklinski MJ, et al. *J Physiol.* 2020;598(14):2817-2834. 3. Ng K, et al. *Circulation.* 2020;142(10):932-947. 4. Peltenburg PJ, et al. *Circulation.* 2022;145(5):333-344. 5. Venetucci L, et al. *Nat Rev Cardiol.* 2012;9(10):561-575. 6. Sibbles ET, et al. *Biophys Rev.* 2022;14(1):329-352. 7. Chen H, et al. *J Gen Physiol.* 2013;142(2):127-136. 8. Bezzerides VJ, et al. *Circulation.* 2019;140(5):405-419. 9. Henriquez E, et al. *Cureus.* 2023;15(10):e47974. 10. Richardson E, et al. *J Genet Couns.* 2018;27(3):549-557. 11. Liu B, et al. In: Zima E. *Cardiac Arrhythmias - Translational Approach from Pathophysiology to Advanced Care*. Published July 14, 2021. Accessed February 9, 2024. https://www.intechopen.com/chapters/77447 12. Dubey N, et al. *Cureus.* 2023;15(10):e47306. 13. Roston TM, et al. *Heart Rhythm.* 2018;15(12):1791-1799.

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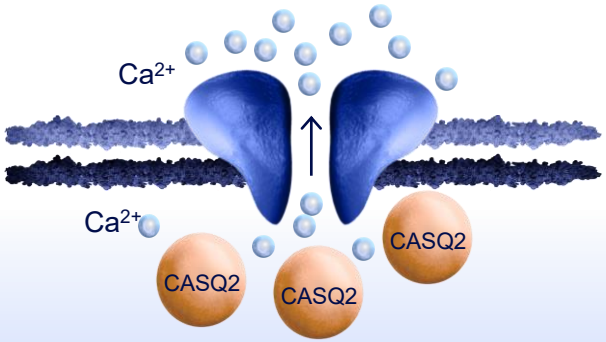
Rationale for CASQ2 Augmentation in RYR2 CPVT

In *RYR2* pathogenic mutations, normal CASQ2 levels are insufficient to maintain RYR2 in a closed conformation during diastole in high Ca^{2+} flux states (such as with adrenaline)

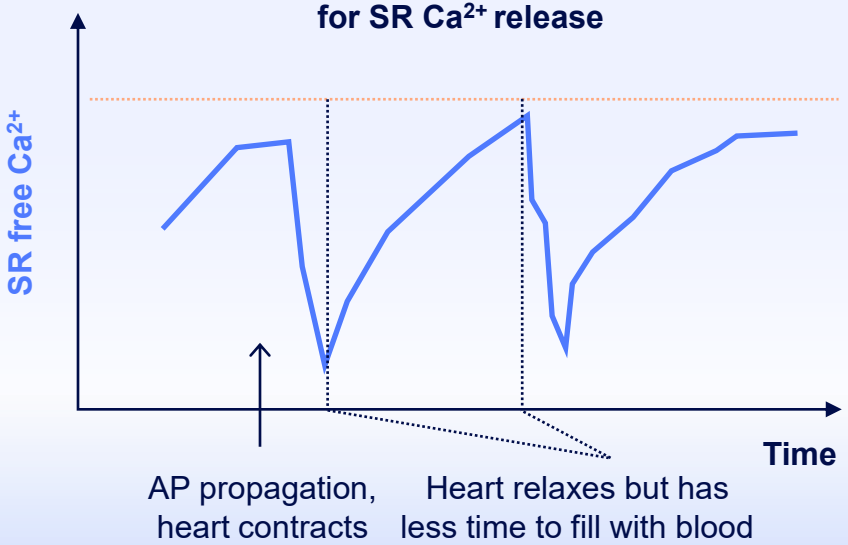
RYR2 Mutation-Related CPVT

Mutations in *RYR2* make the channel more sensitive to SR Ca^{2+} levels. This can result in abnormal release of Ca^{2+} in diastole that can lead to delayed afterdepolarizations (DADs) and resultant ventricular arrhythmia



Arrhythmia

***RYR2* mutations lower threshold for SR Ca^{2+} release**



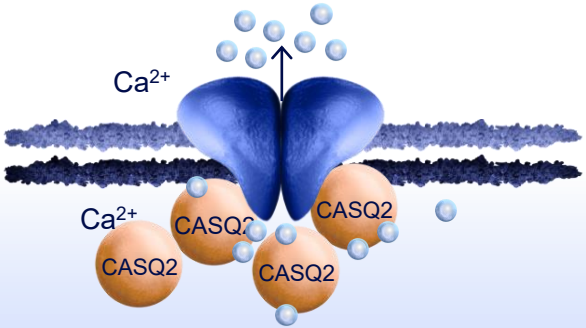
AP=action potential; SR=sarcoplasmic reticulum.
Proprietary data from Priori Lab.

Rationale for CASQ2 Augmentation in *RYR2* CPVT (cont'd)

Cardiac delivery of SGT-501 is intended to increase CASQ2, thus enhancing Ca^{2+} buffering and counteracting Ca^{2+} sensitivity caused by *RYR2* pathogenic mutations

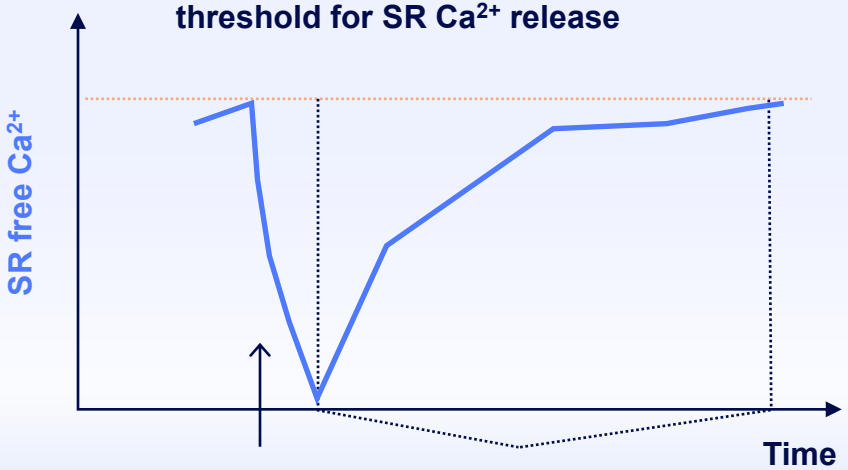
RYR2 Mutation-Related CPVT + Increased CASQ2 Expression

Increased CASQ2 enhances Ca^{2+} buffering within the SR and helps stabilize RYR2 in the closed state in diastole, reducing or eliminating the probability of DADs and resultant ventricular arrhythmia



Normal Rhythm

Increased CASQ2 increases time to reach threshold for SR Ca^{2+} release



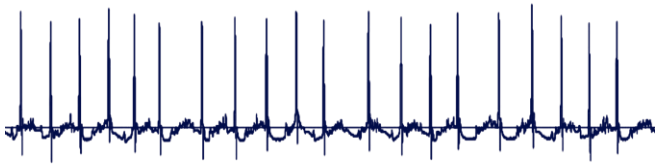
Proprietary data from Priori Lab.

RYR2 CPVT Transgenic Mouse Model Used to Support Proof-of-Concept for AAV Gene Delivery of Human CASQ2

ECG response to β-adrenergic stimulation in 85 days post vehicle or SGT-501 treatment

WT Mice Dosed With Vehicle

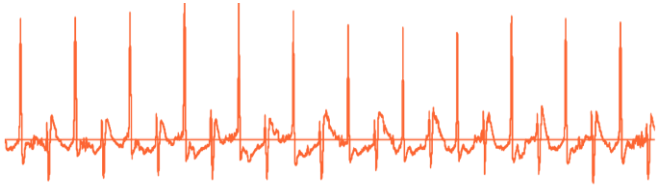
IP dose epinephrine and caffeine



Normal heart rhythm in WT background strain animals

RYR2 Transgenic Mice Dosed With Vehicle

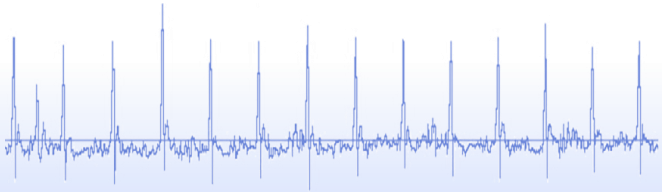
IP dose epinephrine and caffeine



Polymorphic and/or bidirectional arrhythmic morphology in transgenic animals

RYR2 Transgenic Mice Dosed With SGT-501

IP dose epinephrine and caffeine



Normal heart rhythm seen after β-adrenergic challenge in mice treated with SGT-501

ECG=electrocardiogram; IP=intraperitoneal; WT=wild-type.
Data on file. Solid Biosciences 2025.

ARTEMIS Clinical Trial Design: SGT-501 Phase 1b Study

First-in-human, open-label, multi-center study to enroll a minimum of 6 participants.
Activation of first clinical trial site expected Q4 2025

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

Participants

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

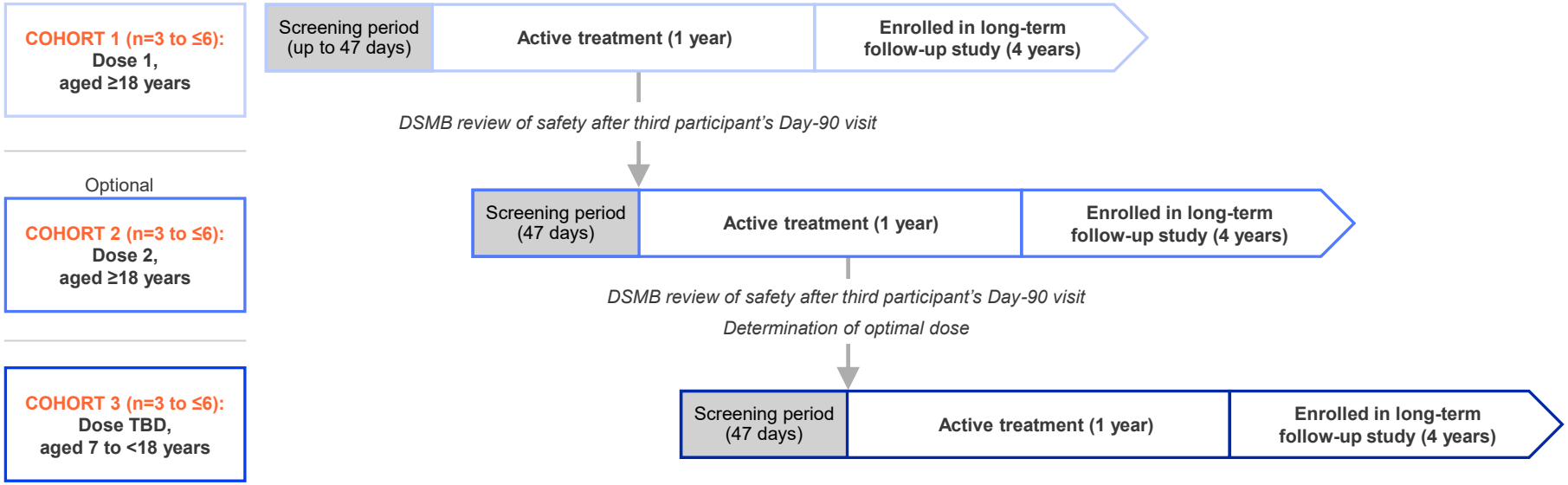
- Change from baseline of VAS on exercise stress test at Day 180

Exploratory Endpoint

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

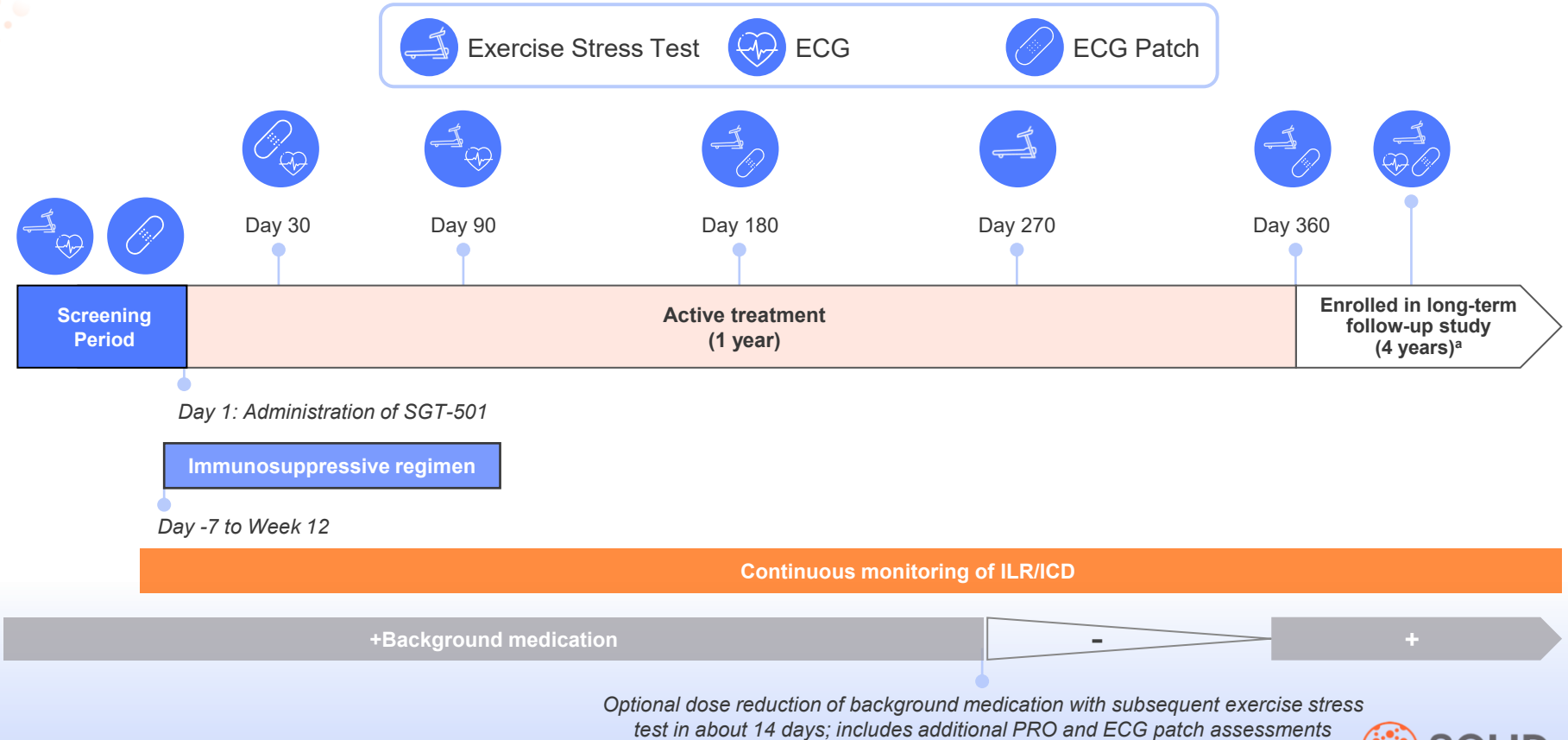
DSMB=data and safety monitoring board; IV=intravenous; TEAE=treatment-emergent adverse event; VAS=ventricular arrhythmia score.
[a]Optional for dose exploration. [b]Based on DSMB recommendation.

Study Schema



At least 3 participants will receive a single IV infusion of SGT-501 in Cohort 1 at a currently undisclosed dose level. To optimize the dose, Cohort 2 (optional) may explore a second dose level, and may only begin dosing following the completion of dosing of at least 3 participants in Cohort 1 and the DSMB review of safety and efficacy data. Cohort 3 may only begin dosing following the completion of dosing of at least 3 participants at the optimal target dose level and the DSMB review of study data from Cohort 1 and Cohort 2 (optional).

Study Visits Schema



ICD=implantable cardioverter defibrillators; ILR=implantable loop recorder; PRO=patient-reported outcome; SCR=screening.
[a]Assessments to be completed every 6 months during long-term follow-up period.

Backup

Main Gene Therapy Trials for Cardiovascular Diseases

Heart Failure With Preserved Ejection Fraction (HFpEF)

Outcome Measure Categories

Arrhythmia | Imaging | Clinical | PRO | Tissue | Exercise | Hospitalization | Lab

SARDOCOR	SARDOCOR	Celladon	Celladon	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
AAV1/SERCA2a for HFrEF (Phase I/II)	AAV1/SERCA2a for HFpEF (Phase I/II)	MYDICAR (AAV1/SERCA2a) for Heart Failure (CUPID) (Phase I/II)	MYDICAR (AAV1/SERCA2a) for Heart Failure (CUPID 2) (Phase IIb)	AAV1-CMV-Serca2a gene Therapy Trial for Heart Failure (AGENT-HF) (Phase II)
Imaging, PRO, Exercise	Imaging, PRO, Exercise	Imaging, PRO, Exercise, Hospitalization	Hospitalization	Imaging, PRO, Exercise, Clinical

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Main Gene Therapy Trials for Cardiovascular Diseases
Ischemic Cardiomyopathy

Outcome Measure Categories

Arrhythmia | Imaging | Clinical | PRO | Tissue | Exercise | Hospitalization | Lab

Kuopio University Hospital	Kuopio University Hospital	XyloCor Therapeutics	XyloCor Therapeutics	YAP THERAPEUTICS
VEGF-D for Severe Coronary Heart Disease (Phase I)	**AdvVEGF-D for Angina Pectoris (ReGenHeart) (Phase II)**	**XC001 for Chronic Angina (EXACT2) (Phase II)**	**Epicardial XC001 for Angina (EXACT) (Phase I/II)**	**YAP101 for Ischemic HFrEF (SALVADOR-HF) (Phase I)**
Imaging, PRO, Exercise	Imaging, PRO, Exercise, Clinical	Imaging, PRO, Exercise, Clinical	Imaging, PRO, Exercise, Clinical	Imaging, PRO, Exercise, Clinical

AdvVEGF-D=adenovirus vascular endothelial growth factor-D; HFrEF=heart failure with reduced ejection fraction; VEGF-D=vascular endothelial growth factor-D.

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Main Gene Therapy Trials for Cardiovascular Diseases

Non-Ischemic Cardiomyopathy

Outcome Measure Categories

Arrhythmia | Imaging | Clinical | PRO | Tissue | Exercise | Hospitalization | Lab

AskBio

Phosphatase Inhibition Gene Therapy for Non-Ischemic Heart Failure (Phase II)