



Creating Novel Therapies
to Treat Cardiovascular
and Orphan Diseases


CORPORATE PRESENTATION

June 2021



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A horizontal banner with a blue-to-dark-red gradient background. It features abstract scientific imagery including a DNA double helix, glowing molecular structures, and a bright light beam cutting through the scene.

Developing novel cardiovascular and metabolic treatments that bring meaningful therapeutic value to patients with unsatisfied medical needs in cardiovascular and/or rare diseases

INVESTMENT HIGHLIGHTS



Pivotal Phase 3 clinical trial underway in Systemic Sclerosis (SSc), **an orphan disease with no FDA approved treatments**, representing a blockbuster market opportunity



Robust pipeline of novel medicines addressing unmet needs in **cardiovascular and orphan diseases**



Seasoned leadership team **with strong track record** in drug discovery, development and successful commercialization of therapies



Supported by consortium of top U.S. and corporate VCs, led by **Boxer Capital, Roche Ventures, Tang Capital, RA Capital and a leading NYC-based biotechnology investment fund**

CLINICAL DEVELOPMENT PIPELINE

Robust clinical pipeline with mix of late-, mid- and earlier stage programs

Drug	Target	Rt of Admin	Indication	Development Stage				
				Pre-clin	Phase I	Phase II	Phase III	Commercial
Iloprost	IP-Rec.	I.V.	Systemic Sclerosis					
CIVI 008	PCSK-9	Oral	Lipid disorders					

EXPERIENCED MANAGEMENT TEAM



Shal Jacobovitz
Chief Executive Officer

- 30+ years experience in pharma industry leadership roles (Actelion U.S., F. Hoffman LaRoche, Abbott Canada, Nordic Labs & Marion Merrill Dow [now Aventis])
- Former CEO of the American College of Cardiology (2013-2018)
- Former President of Actelion US (2004-2013), acquired by J&J for \$30B



Henrik Oerum, MD, MSc
Chief Scientific Officer

- 25 years as biotech entrepreneur and pharma executive (Boehringer Mannheim & Hoffmann-la Roche)
- Led development of LNA antisense drug platform at Santaris that discovered the CIVI 007
- Founder of CIVI Biopharma, Santaris Pharma & Exiqon



Chuck Shear, DrPH, FAHA, FACC
Chief Development Officer

- 30+ years experience in pharma industry in CV therapeutic area development leadership roles (Merck, Pfizer, CLS Behring) including lipid-lowering programs; statins, CETP, HDL infusion and PCSK9



Wade Benton, PharmD
Vice President, Clinical Development

- 20 years experience in drug development and academic research in Systemic Sclerosis, PAH, Cystic Fibrosis, Pediatric Critical Care
- 15 years experience developing and commercializing prostacyclin analogs
- Founder and CEO of Eicos Sciences, Inc



Dinesh Khanna, MD, MSc
Medical Lead for Scleroderma Dev.

- Frederick G.L. Huetwell Professor of Medicine and Director, University of Michigan Scleroderma Program
- Member of American College of Rheumatology and recipient of the Henry Kunkel Young Investigator Award.
- Published over 350 peer-reviewed articles and book chapters



Kevin Christal
Vice President, Operations & Planning

- 18 years experience in commercial operations and business development spanning numerous disease areas
- 15 years experience developing and commercializing prostacyclin analogs
- Co-founder and COO of Eicos Sciences, Inc.



CIVI 030 (IV Iloprost)

A potent vasodilator and platelet inhibitor with anti-inflammatory and anti-fibrotic effects in development for the treatment of Systemic Sclerosis (SSc)

DIGITAL ISCHEMIA IN SSC REPRESENTS A CONTINUUM THAT CAN PROGRESS FROM RAYNAUD'S PHENOMENON TO CRITICAL DIGITAL LOSS



Raynaud's Phenomenon; experienced by 95% SSc patients

- SSc greatly exacerbates normal vasoconstrictive response to cold/stress
- Symptomatic attacks can be extremely painful and accompanied by numbness, tingling, and loss of dexterity

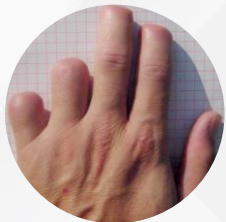


Digital Ulcers; 58% patients w/30% annual prevalence

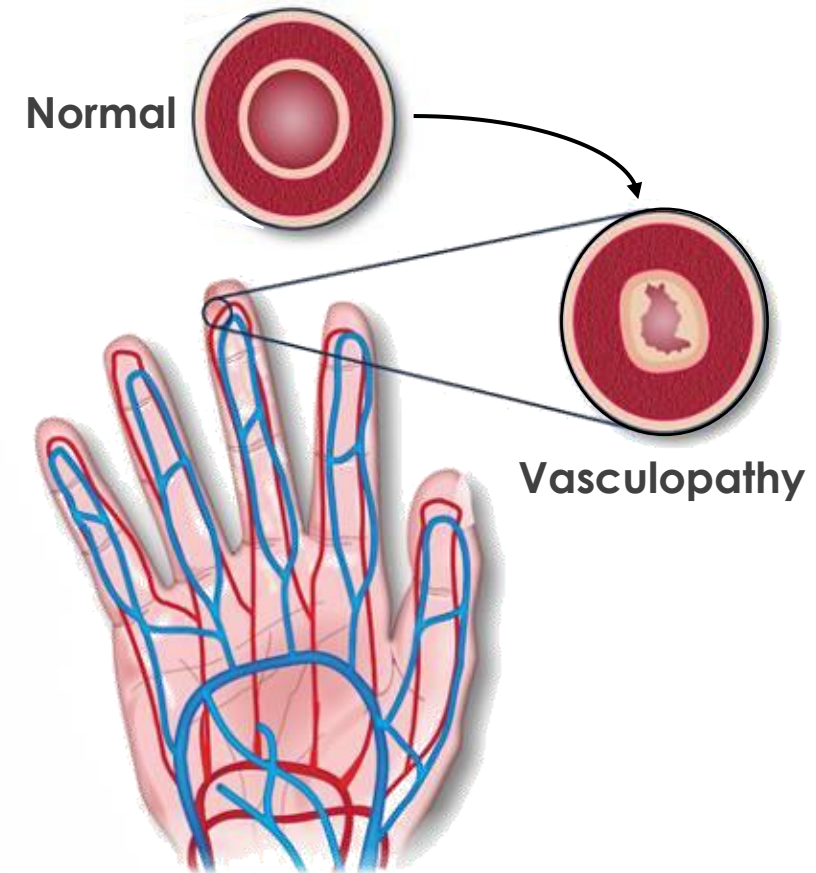
- Necrotic lesions occurring at distal aspects of digits
- Can result in amputation, hospitalization, infection, gangrene



Gangrene in 10%, Infection in 26% over 2 years in patients with history of DUs (DUO Registry)¹



Amputation in 16% over 2 years in patients with chronic DUs¹



SSc results in digital ischemia due to progressive occlusive vasculopathy with compromised vessel lumen

¹Matucci-Cerinic M, Krieg T, Guillevin, et al. Ann Rheum Dis 2016; 75:1770-1776.

SUBSTANTIAL CLINICAL DATA SUPPORTING EFFICACY AND SAFETY OF INTRAVENOUS ILOPROST IN SSC



Multiple studies over past 30 years demonstrating efficacy and safety of IV iloprost in SSc-related vasculopathy (Raynaud's and digital ulcer healing)



Most frequently administered as a 6-hour continuous infusion on 5 consecutive days with benefits lasting up to 9 weeks post infusion



EU approval for RP based primarily on DBPC study in SSc (n=131) demonstrating improvement in RP attack frequency vs placebo (p<0.01)

No FDA approved treatments for SSc-vasculopathy with SOC in US; primarily limited to lifestyle modifications and off-label oral vasodilators (CCB, PDE5)

DIGITAL ISCHEMIA IN SSC HAS A SUBSTANTIAL IMPACT ON PATIENT QOL



“

If you can imagine a labor pain in your fingers, it's like in between it's fine, but when it's there it's like oh, my gosh, it really takes all your attention

Open ulcerations are the most miserable thing. The only thing I can compare it to is if you [have a] paper cut and pour lemon juice in it...For me, when my Raynaud's causes the open ulcerations that's a 24/7 issue for me

Think of everything you do with your hands and Raynaud's affects it

”

THE LARGEST DBPC¹ STUDY FOR IV ILOPROST IN SSC SHOWED A ROBUST TREATMENT EFFECT ON SSC-RP ATTACK FREQUENCY AND SEVERITY

Study	Design	N	Treatment Dose & Duration	Baseline weekly attack	RP Attack Frequency Results	RP Severity Score Results
Wigley et al, 1994	RCT [active-pbo parallel]	131	0.5-2.0 ng/kg/min 5 days	<ul style="list-style-type: none"> 28 Active 27 Placebo 	<p>Percent reduction from Weeks 1 to 3</p> <ul style="list-style-type: none"> – 34% for iloprost (p=0.002) – 16% for placebo <p>Percent reduction over Weeks 1 to 9</p> <ul style="list-style-type: none"> – 39% for iloprost (p=0.005) – 22% for placebo 	<p>Percent reduction from Weeks 1 to 3</p> <ul style="list-style-type: none"> – 31% for iloprost (p=0.006) – 13% for placebo <p>Percent reduction over Weeks 1 to 9</p> <ul style="list-style-type: none"> – 35% for iloprost (p=0.01) – 20% for placebo

Intravenous Iloprost Infusion in Patients with Raynaud Phenomenon Secondary to Systemic Sclerosis: A Multicenter, Placebo-controlled, Double-Blind Study

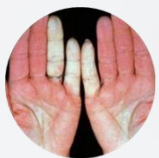
Fredrick M. Wigley, MD; Robert A. Wise, MD; James R. Seibold, MD; Deborah A. McCloskey, RN; Gregory Kujala, MD; Thomas A. Medsger, MD; Virginia D. Steen, MD; John Varga, MD; Sergio Jimenez, MD; Maureen Mayes, MD; Philip J. Clements, MD; Steven R. Weiner, MD; John Porter, MD; Michael Ellman, MD; Christopher Wise, MD; Lee D. Kaufman, MD; John Williams, MD; William Dole, MD

¹ DBPC: Double-blind placebo controlled

PHASE 3 TRIAL IS UNDERWAY AT US SITES



A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study Evaluating the Safety and Efficacy of Intravenous Iloprost in Subjects With Systemic Sclerosis Experiencing Symptomatic Digital Ischemic Episodes



Primary Endpoint

Change of symptomatic digital ischemic episodes, as measured by weekly frequency of symptomatic Raynaud's attacks



Sites

~30 US sites



Sample

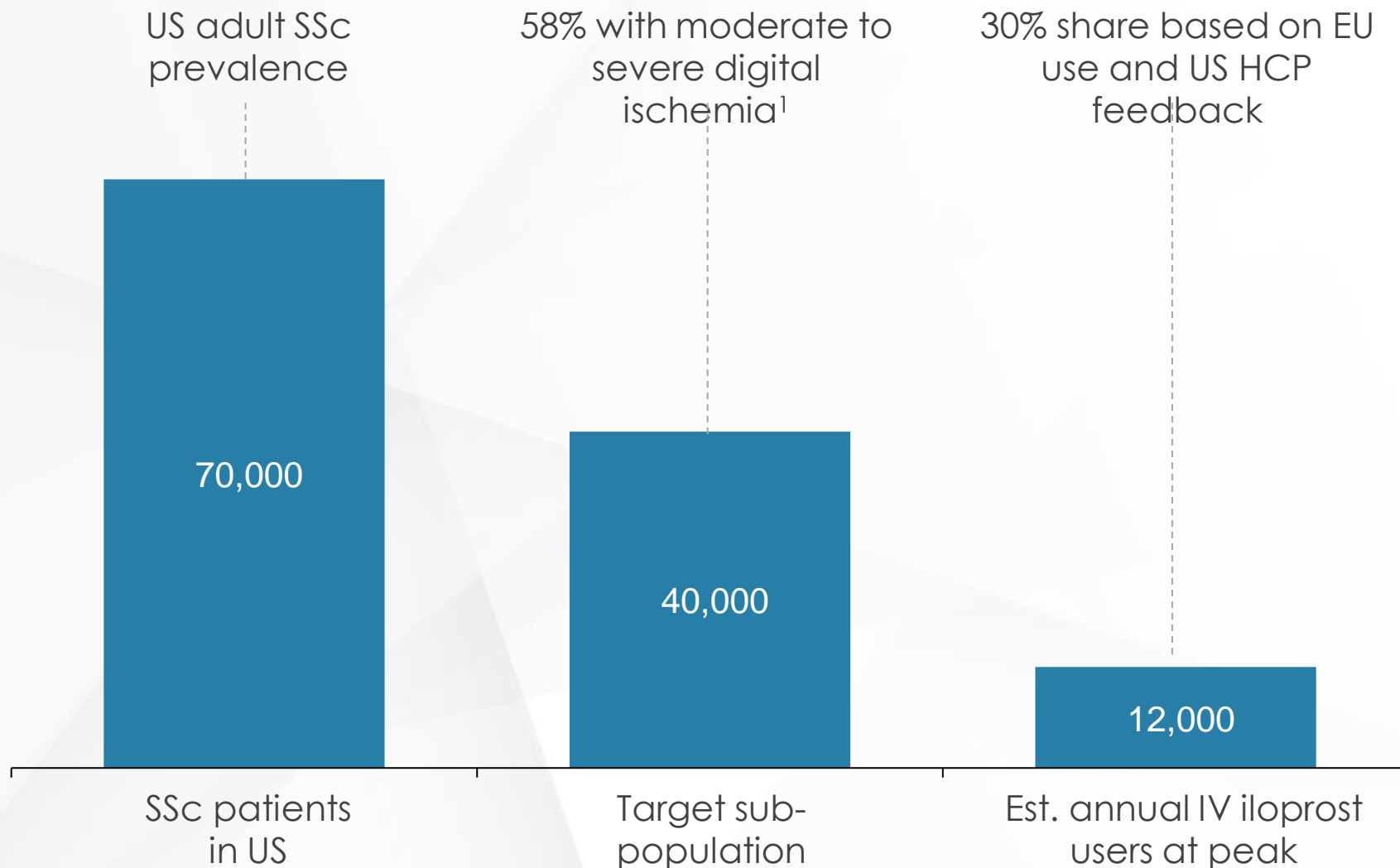
Up to n=180



Topline Data

Mid-2021

SIGNIFICANT REVENUE POTENTIAL WITH RAPID UPTAKE ANTICIPATED



¹ Overall incidence of digital ulcers used as proxy to estimate proportion of patients with moderate to severe digital ischemia

Favorable initial pricing feedback with peak revenue opportunity ~\$1B

FAVORABLE PRICING RANGE BASED ON INITIAL PAYER FEEDBACK AND ANALOGUES



Initial payer feedback suggests favorable pricing in-line with specialty rheumatology analogues



Administration profile will self-limit product to patients deriving significant benefit

Rheumatology Large Market

- RA, Psoriasis: JAK inhibitors, IL-23/17, TNFs
- ~\$60k up to \$90k

Prostacyclin class for PAH

- \$200k+

Rheumatology specialty

- Nintedanib; SSc-ILD: \$120k
- Pegloticase; gout: \$200k+

MARKET DYNAMICS WILL ALLOW FOR EFFICIENT TARGETING AND RAPID UPTAKE AT LAUNCH



Concentrated network of centers treat a high proportion of SSc patients



Majority of key centers are participating in Phase 3 program



High level of enthusiasm and familiarity with IV iloprost among US KOLs



Very motivated patient population with limited treatment options

WITH A POSITIVE PHASE 3, COMMERCIAL LAUNCH ANTICIPATED 2022 WITH PRIORITY REVIEW

2021

AURORA Phase 3 LPFV

AURORA Topline Results

NDA Submission



NDA submission via 505(b)(2) regulatory pathway using Ventavis (inhaled iloprost) and iloprost literature to support safety



FDA Orphan Drug Designation (ODD) for iloprost for the treatment of Systemic Sclerosis received May 2019

2022

PDUFA with Priority Review

PDUFA with Standard Review




ODD provides 7 years market exclusivity from time of NDA approval




CIVI 008

A long-acting, third generation PCSK9 in development for treatment of hypercholesterolemia and prevention of atherosclerotic cardiovascular disease (ASCVD)

CVD REMAINS A LEADING CAUSE OF DEATH GLOBALLY¹

 Elevated LDL-C causes ASCVD and statin therapy remains as SOC treatment.²

 Statin therapy will not always provide for optimal LDL levels (insufficient intensity, intolerance, non-compliance); estimates range from 36-80%.^{3,4}

 PCSK9s (mAb's) provide unprecedented LDL-lowering, have proven clinical benefit and are poised to revolutionize therapeutic prevention of ASCVD.

 High prices and inconvenient dosing regimens remain significant barriers to broad PCSK9 use.

CIVI 008 has potential to combine mAb-like LDL efficacy with the improved dosing convenience of an oral and at a low cost of goods

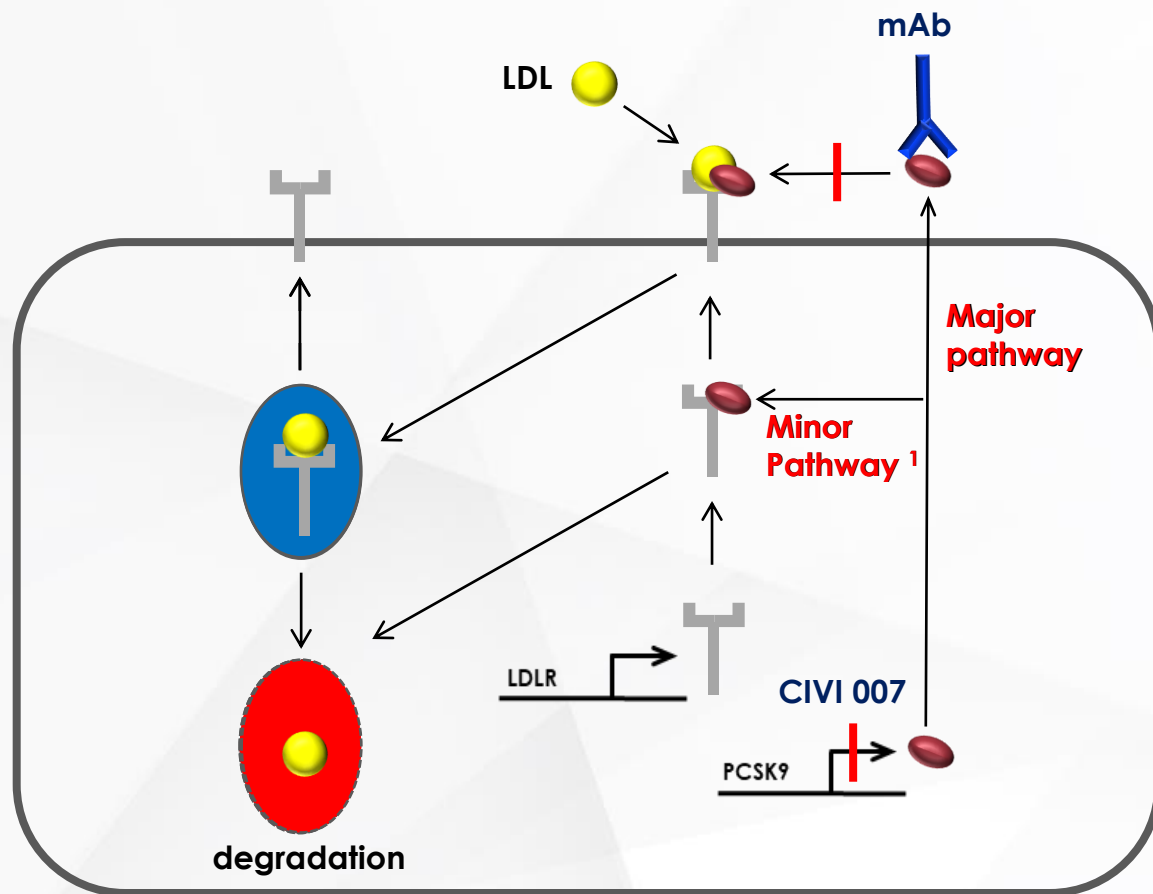
¹ Heart Disease and Stroke Statistics—2019 Update. Circulation 2019; 139: e56-e528

² Lee et al JAMA Cardiol. 2016;1; 700-7

³ Toth et al. Am J. Cardiovasc Drugs 2018 18: 157-173

⁴ Ballantyne CM, et al. Am Heart J 2005;149:464-73.

CIVI 008 MOA: COMPARISON TO APPROVED ANTI-PCSK9 MAB'S



Major PCSK9 outcome studies demonstrate increased benefits of achieving LDL levels significantly below current treatment targets



Improved Lipid lowering compared to mAbs



MoA more similarly mimics LoF mutations than mAb's, and may translate into improved outcomes



Plasma ceramide profile (linked to reduced CV-risk²), more similar to human LoF than mAb profiles.



Improved Lipid lowering in mAb non-responders due to mutations on PCSK9 binding site

¹ Lagace Curr Opin Lipidol (2014) 25: 387-393

² Data on specific serum markers for "ACS event survival" (Zora Biosciences) suggests that certain ceramides are highly predictive markers of outcome. Profiles from PCSK9 KO mice and human carriers of PCSK9-LoF are very similar and distinct from profiles in mAb treated patients.

CIVI 008: TARGET PROFILE FOR HIGH RISK ASCVD

CIVI 008 targets maintenance of the durable efficacy of MABs with a more convenient and cost-effective profile

	CiVi 008 (Target Product Profile)	mAbs	Inclisiran
LDL Reduction	Stable and robust LDL reduction of >60% throughout the dosing cycle	(~60% and stable through the dosing cycle)	~50% time averaged reduction with return towards pre-treatment level by end of dosing cycle
Safety Profile	Well tolerated and acceptable safety profile	✓	✓
Dose and route of administration	Daily Oral	Subcutaneous injection only: every two weeks or monthly by multiple injections or on-body infusion	Subcutaneous injection only: day 1, month 3 and every 6 months thereafter
COGS	Best-in-class COGS	X	X

SIZEABLE MARKET OPPORTUNITY FOR ORAL PCSK9 IN SECONDARY PATIENTS

Market Segmentation				Patients on Statin Not Achieving Target ¹ (2031)	CiVi Oral Share ¹	CiVi Patients (2031)	Price	CiVi Market Size
POPULATION WITH ELEVATED LDL-C ¹ (35% of Adult Population in USA 250 Million in 2025)	NON-FAMILIAL (99%)	PRIMARY (42%) ³	LOW RISK					
			HIGH RISK					
		SECONDARY (58%) ³	LOW RISK LDL 70-100	5.8 Million	10%-15%	580K-870M	\$2k-\$3k	\$1.2B-\$2.6B
			HIGH RISK LDL>100	5.8 Million	25%-30%	1.45M-1.74M		\$2.9B-\$5.2B
	FAMILIAL ² (both HeFH and HoFH)	ALL	ANY	112 Thou.	35%	39 K		\$78M - \$117M
		Total	11.7 M	17%-22%	2.1M-2.6M	\$2k-\$3k	\$4.2B - \$7.8B US	

1. 8.2 million on Statin * 70.5% of patients "not controlled" (Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association Emelia J. Benjamin et al., Circulation March 6, 2018, Volume 137, Issue 10)

CORPORATE & FINANCIAL SNAPSHOT



Private company founded in 2017



Offices in Washington, DC and San Francisco; 17 FTEs



Orphan Drug exclusivity for lead product, CIVI 030
CIVI 008 has long-lived composition of matter patents worldwide (2034)



Leading venture and corporate investors (Leading NYC-based biotechnology investment fund, Boxer Capital, Roche Ventures, RA Capital and Tang Capital)
Raised ~\$120 million to date

RECENT / UPCOMING MILESTONES



Complete oral formulation of CIVI-008



Complete enrollment of Phase 3 study of CIVI-030 in SSc



Complete NHP, toxicology and file IND for CIVI 008



Complete manufacturing of registration batches for CIVI 030



Topline data readout from CIVI 030 Phase 3 AURORA study



Initiate Phase 1 Studies of Oral PSCK9 – CIVI 008



NDA Submission of CIVI 030 as a treatment for SSc



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