BIOPHARMA / CARDIOVASCULAR, ENDOCRINE DISORDERS & INFECTIOUS DISEASE

LEERINK PARTNERS

Cardiology Primer: Positive Revival in Drug Development Converges on Unmet Need

March 24, 2025

Reason for report:
PROPRIETARY INSIGHTS

S&P 500 Health Care Index: **1,703.97**

Companies Highlighted

AMGN, ARWR, AZN, BMY, CYTK, EWTX, IONS, LLY, LXRX, MRK, NAMS, TECX, TRML

- **Bottom Line: We believe Cardiology represents an increasingly attractive therapeutic area with mounting large pharma interest and commitment, driven by a blend of high unmet need and positively evolving trends that suggest new blockbuster opportunities are still "in play" for emerging cardiology therapies and companies.** Everything we learned from attending major cardiology meetings, speaking to KOLs deeply involved with cardiology drug development and clinical trials, and interacting with public and private biotechs in the space points to three important things that we believe are different for cardiology vs ~10-15 years ago: a) appetite for investing in cardiology assets has improved, b) cardiovascular (CV) trial design and clinical endpoints are getting more efficient, and c) multiple large pharmas have kept a foothold in cardiology, and could be primed to "lean into it" more in the future. In this backdrop, we are optimistic about the future outlook for the cardiology sector, and while this primer is not exhaustive, it does provide a foundation for investors to unpack major industry themes we're seeing, example cardiology case studies, and how the cardiology/CV field could evolve ahead.
- **Our analysis highlights multiple reasons to be excited about drug development in cardiology / cardiovascular areas, including: (1)** cardiovascular disease (CVD) has a significant global footprint (~523M patients worldwide, ~7% of total population) combined with high healthcare costs (projected >$1 trillion market by 2035), creating large commercial opportunities, **(2)** looming loss of exclusivity (LOE) for CV blockbusters (Eliquis, Entresto, Xarelto, Brilinta) in the next ~5 years could motivate large pharmas to revamp their cardiology portfolios, **(3)** historical M&A interest in cardiology reflects significant premiums (MyoKardia: ~61% premium, CinCor: ~206% premium) and exhibits high pharma interest in differentiated cardiology/CV assets, and **(4)** the evolving regulatory landscape could create more flexible development paths in the future. For example, we think heart failure is a subsector to watch as 2019 FDA guidance [LINK] suggests interest in approving drugs based on symptomatic and functional improvement rather than traditional mortality benefit (details within).
- **We are especially excited about the following themes for 2025: (1)** A new class of emerging therapies targeting Lp(a) for CV risk reduction has been a hot topic for investors (our KOL note HERE)—while NVS' [Not Rated] Ph.3 HORIZON trial for pelacarsen was delayed to 2026, we see this as a critical catalyst that could validate the "Lp(a) hypothesis" and potentially drive value for multiple companies with Lp(a)-targeting assets (i.e., NVS, AMGN [MP, Risinger], LLY [OP, Risinger], IONS [OP, Foroohar], ARWR [MP, Foroohar], AZN [OP,

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Berens], SLN [Not Rated], NAMS [OP]). **(2)** Additionally, the evolving landscape for HFpEF (heart failure with preserved ejection fraction) and adjacent indications presents another significant opportunity, with multiple novel mechanisms and strategies being explored beyond SGLT2i's such as TECX [OP, Risinger] for PH-HFpEF, BMY [OP, Risinger] and CYTK [OP] with pipeline assets targeting HFpEF, as well as ARWR, AMGN, and TEVA [Not Rated] with emerging mechanisms targeting inflammation, fibrosis, and metabolic pathways in HFpEF, among others.

- **Continued inside, we seek to address the following investor questions: (1)** Why are pharmas committed to cardiology/CV? **(2)** Why are pharmas coming back to cardiology/CV? **(3)** What is pharma's commercial strategy in cardiology? **(4)** What are targets of interest right now? **(5)** What does updated FDA guidance mean for heart failure (HF) drug development? **(6)** What are important cardiology/CV clinical trial endpoints to know?

Key Highlights From Our Analysis of the Cardiology Sector:

(1) Why Are Pharmas Committed to Cardiology/CV?

- **We believe the combination of high disease prevalence, significant economic burden, and improved diagnostic capabilities creates a compelling and expanding market opportunity that continues to attract pharmaceutical companies focusing on and exploring CV therapeutics.** Specifically, cardiovascular disease (CVD) represents a significant global burden with substantial economic impact. CVD affects approx. ~523M people globally, representing one of the most prevalent disease states worldwide, and it causes roughly one-third of all global deaths. Looking ahead, CVD prevalence is expected to increase significantly, particularly in the US where projections suggest nearly half of Americans could be affected by 2035. The economic burden is equally staggering, in our view, with US healthcare spending on CV diseases outpacing most European nations, driving a projected US market opportunity potentially exceeding $1 trillion in the coming decade. Notably, approx. ~20% of adults worldwide have elevated LDL-C levels above recommended thresholds despite widespread statin use, while elevated Lp(a) affects approx. ~20-30% of the global population (>1.4 billion people), representing a significant under-treated CV risk factor. Biotechs like NAMS are pursuing this market opportunity in a differentiated way, having recently entered the space with innovative approaches to address substantial unmet need for more potent and safe lipid-lowering therapies, particularly targeting persistent LDL-C elevation and unaddressed high Lp(a) levels, where traditional treatments have fallen short. Going forward, as advanced diagnostic testing becomes more widely available and integrated into primary care, we anticipate increased identification of novel risk factors, particularly Lp(a) which has historically been under-diagnosed. **See pages 7-8** within for more detail.

(2) Why Are Pharmas Coming Back to Cardiology/CV?

- **Major CV blockbusters are facing imminent patent cliffs, which we think could motivate pharmas to revamp their cardiology/CV portfolios.** Several cornerstone CV treatments including Eliquis, Entresto, Xarelto, and Brilinta will lose exclusivity over the next few years, creating, in our view, urgency for large pharmas to rebuild their CV franchises and pivot existing CV-related resources to a novel or next-gen CV product. This catalyzed M&A activity in the past, with companies demonstrating willingness to pay high premiums for more innovative assets—notably BMY's acquisition of MyoKardia and AZN's strategic purchase of CinCor at more than triple its prior stock value. It also appears that more "established" CV players like NVS (Not Rated) and AZN are actively reinvesting in the space with novel mechanisms and modalities (i.e., NVS' recent acquisition of Anthos [LINK]). Further, the dramatic increase in cardiology/CV clinical trials over the past two decades further validates this renewed interest. Beyond traditional CV targets, we see two interesting opportunities emerging: HFpEF and atrial fibrillation (AFib). HFpEF represents approx. half of all heart failure cases (affecting ~3M patients in US) but has historically proven resistant to therapies that work in reduced ejection fraction heart failure. With the therapeutic regulatory path moving towards more flexibility and SGLT2i's demonstrating modest benefits, we see tremendous opportunity for novel mechanisms that more directly address underlying disease pathophysiology. We note HFpEF is also gaining momentum

among private biotechs, with companies like Cardurion [private] investigating novel assets in Ph.2. Similarly, AFib affects over ~33M people globally with substantial projected growth as populations age, yet current treatments focused primarily on rate/rhythm control and anticoagulation leave significant unmet needs in disease modification and prevention. We also note growing interest in uncontrolled hypertension, with companies like Kardigan [private] and Mineralys [MLYS, Not Rated] pursuing this area of unmet need with differentiated assets. In all, these large, underserved markets represent particularly attractive opportunities for CV-focused companies to develop transformative therapies. **See pages 9-11** for more detail.

(3) What is Pharma's Commercial Strategy in Cardiology?

- **We note that commercial approaches in cardiology are shifting from broad primary-care models to targeted specialty strategies, which we think is a good sign for the space.** We're particularly seeing a movement from "brute force" primary care launches defined by large field forces and high resource spend to more targeted specialty cardiology approaches with efficient, specialized teams and precision marketing. This transition includes greater emphasis on digital outreach and targeting cardiology networks/thought leaders via scientific channels rather than costly mass advertising. CYTK reflects this approach with its development of aficamten for hypertrophic cardiomyopathy (HCM), where the company is strategically building a specialized sales team focused exclusively on HCM centers of excellence. CYTK's targeted strategy allows for deeper engagement with the ~200 specialized centers that diagnose and manage the majority of HCM patients, creating opportunities for more efficient market penetration and potentially accelerated patient identification. Companies are also increasingly prioritizing specific, high-risk populations requiring precision treatment rather than pursuing broad, generalized patient groups. As cardiology moves toward more personalized medicine, we expect continued commercial innovation with multiple entry points for differentiation even in seemingly established markets —whether through patient selection tools, digital engagement platforms, or specialized physician networks. This evolution better aligns with the increasingly specialized nature of cardiology care and the emergence of more targeted therapies requiring specialist management, creating multiple avenues for companies to drive value in large cardiology markets despite potential competition. **See page 12** for more detail.

(4) What Are Targets of Interest Right Now?

- **There are many targets that we find intriguing, and in this report we highlighted several examples that fall into two groups—"renaissance" vs "novel" targets—which each offer companies diverse opportunities in CV drug development.** We've seen a surge in previously studied mechanisms that are "rediscovered" and re-interrogated today for cardiology/CV applications, including Lp(a), Factor XI, PDE9, CAMKII, S1P Receptor Modulators, and MR. Simultaneously, emerging mechanisms with potential in CV diseases are gaining traction, such as PARP (cardioprotection during ischemia), ANGPTL3/4 (lipid metabolism), etc. Of interest is the large market opportunity in Lp(a) as a causal CV risk factor distinct from traditional lipid pathways, with multiple companies developing therapies (NVS, AMGN, LLY, IONS, AZN, SLN, NAMS). While Novartis' HORIZON CV outcomes trial for pelacarsen was delayed to 2026,

we see this as a critical catalyst that could validate the "Lp(a) hypothesis" and potentially generate significant value for companies targeting this novel risk factor. And furthermore, we don't think "the road ends with Lp(a)" in cardiology—there are likely other mechanisms "in the wings" that we believe could rise up as equally exciting with additional validation and biopharma development. One such category of targets we're watching is in the cardio-immunology realm, including companies focusing on IL-6 (TRML [OP, Smith], NVO [Not Rated]) and next-gen CD47 inhibitors (i.e., Bitterroot Bio [private]). **See pages 15-16** for more detail.

(5) What Does Updated FDA Guidance Mean for HF Drug Development?

- **We think the 2019 FDA draft guidance for Heart Failure (HF) sets a foundation for more flexible development pathways for HF-focused therapeutics, and it could signal a favorable regulatory trend that might benefit other high unmet-need, blockbuster cardiology indications.** The FDA guidance suggests that drugs improving symptoms or physical function, without necessarily showing favorable effects on survival/hospitalization, could potentially be approved for heart failure. This represents a shift toward greater emphasis on symptom relief and functional improvement as valuable endpoints, potentially accelerating development timelines and reducing trial costs. Importantly, we believe this creates more flexibility for developing novel therapies for heart failure with preserved ejection fraction (HFpEF), where mortality benefits have historically been difficult to demonstrate, while symptomatic improvement remains a critical unmet need. We note that this FDA guidance states that "a drug that improves symptoms or function when added to standard of care would be valuable even if it did not improve survival or hospitalization," creating new opportunities for companies developing HFpEF therapies. **See pages 17-19** for more detail.

(6) What are important Cardiology/CV Clinical Trial Endpoints to Know?

- **Cardiology/CV endpoints that are well-established and increasingly focused on span clinical outcomes and patient experience, and herein we highlight ones we think investors should know as they explore the space.** Major Adverse Cardiac Events (MACE: CV death, MI [myocardial infarction], stroke) remains the gold standard for CV outcomes trials (CVOTs), with upcoming readouts including Ph.3 PREVAIL (NAMS' CETPi obicetrapib, estim. 2H26 readout), Ph.3 CORALreef (MRK's [OP, Graybosch] oral PCSK9i MK-0616, estim. 2029 readout) and Ph.3 HORIZON (NVS' Lp(a) asset pelacarsen, estim. 2026 readout), among others. And, patient-reported outcomes like KCCQ are gaining importance particularly in the HCM arena, with anticipated data from Ph.3 SONATA (LXRX's [MP] sotagliflozin, estim. late 2026/early 2027 readout) and Ph.3 ACACIA (CYTK's aficamten, 2026 readout by our estimate). Functional capacity metrics like peak oxygen consumption (pVO2) are also increasingly recognized, with Ph.3 MAPLE (CYTK's aficamten, estim. 1H25 readout). We see continued emphasis on outcomes trials in CV drug development, with the benefit of smarter execution and more efficient trial designs, reflecting a desire to pursue blockbuster opportunities while demonstrating real-world patient benefits and long-term efficacy, which we think is crucial for both regulatory approval and long-term market success. **See page 21** for more detail.

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1 Why Are Pharmas Committed to CV? Solving High Healthcare Costs, Rising Prevalence, Socioeconomic Factors Continue to Retain Large Pharma Interest

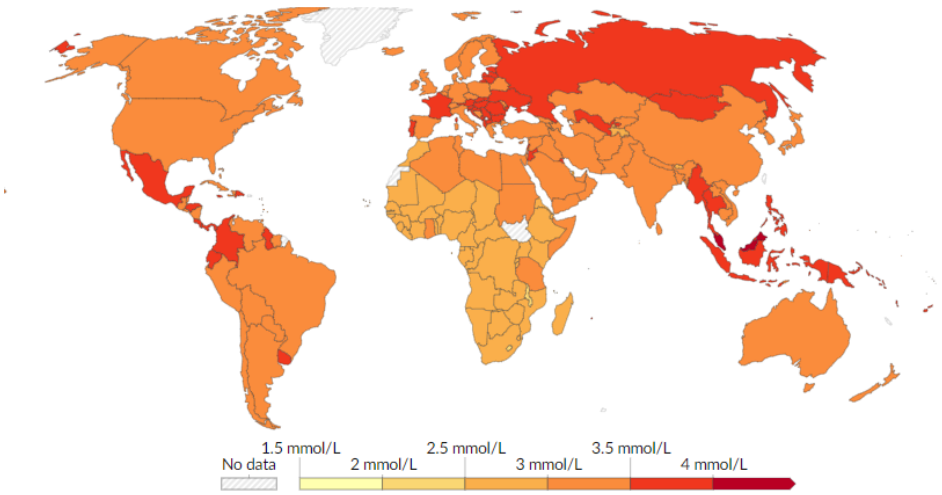
Cardiovascular disease (CVD) has a major worldwide impact:

- Affects an estimated ~523M people globally, representing ~7% of the total population
- Remains the leading cause of death globally, representing ~33% of all global deaths
- The prevalence of CVD in the US is projected to rise from 41.5% in 2015 to 45.1% by 2035, affecting ~131M Americans

More than 1 in 3 adults in the US live with one or more types of cardiovascular disease

- Common CV risk factors include: A) Hypertension, B) High cholesterol, C) Obesity, D) Diabetes, E) Smoking, F) Physical inactivity

National Age-Standardized Mean Non-HDL Cholesterol



CVD and its Risk Factors: A Global Perspective

- Hypercholesterolemia **affects estimated ~39% of adults worldwide**
- Current guidelines recommend treatment in all persons at 3.3 mmol/L and moderate to high-risk persons at 2.6 mmol/L
- Novel therapies targeting inflammation, triglycerides, and other risk factors are needed to complement cholesterol-lowering treatments

US Mortality Rates by Disease Type

Specifically, Cardiovascular Disease Remains a Critical Health Concern in the US

- Cardiovascular disease remains the **leading cause of death** in the US, with a **50% higher mortality rate** than that of cancer, the second most prevalent cause
- CVD accounts for approximately **1 in every 3 deaths in the US**
- CVD risk factors are highly prevalent in the US, with half of adults having hypertension, 42% classified as obese, and 10.5% of the population living with diabetes

Source: Company Reports, Leerink Partners Research, Evaluate, (1) WHO Fact Sheet 2021, (2) CDC Heart Disease Facts 2022, (3) Virani et al, *American Heart Association*. 2023, (4) GBD 2020 Risk Collaborators Report; CVD=cardiovascular disease; HDL=high-density lipoprotein, CV=cardiovascular

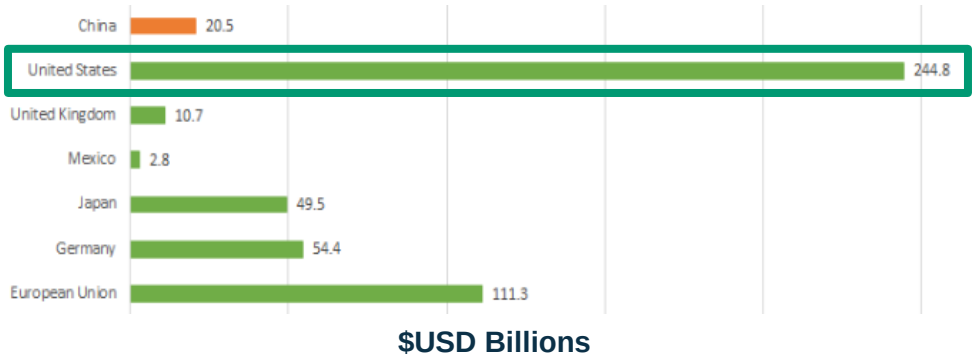
1 **Why Are Pharmas Committed to CV?** Solving High Healthcare Costs, Rising Prevalence, Socioeconomic Factors Continue to Retain Large Pharma Interest

Cardiovascular healthcare costs differ significantly between the US and EU/ROW countries

- Healthcare spending on cardiovascular diseases in the **US is ~2-3 times higher per capita** than in most European countries
- This disparity is likely driven by **higher drug and medical device prices in the US**, more intensive use of technology and interventional procedures, higher testing rates, and increased administrative costs

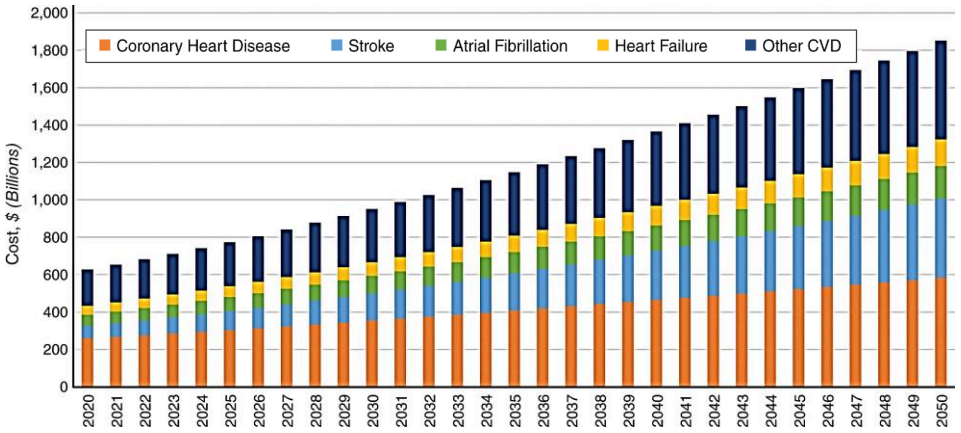
Given the rising prevalence of CVD, the expected market size for all CV disorders could be over $1 trillion by 2035

Annual Cost of CVD by Country in 2019



- CVD represents 1 in 6 US healthcare dollars, with **10-year patient costs reaching over ~$23K,** 78% of which is spent on medications
- With countries like Japan & Germany also incurring high annual costs ($49.5B and $54.4B, respectively), there is **rising global demand for effective CVD treatments and preventive measures**
- High global disparity in CVD treatment costs, with **high-income countries spending $169 per capita** annually, vs only **$4 per capita in low-income countries** (a 42-fold difference)

Estimated Population-level Economic Burden of CVD & Stroke in US Adults



- The **CAGR** for CVD and stroke from 2020 to 2050 is **3.65%**
- Given the rising prevalence of cardiovascular disease, the **expected market size for all cardiovascular disorders projected to reach ~$2 trillion by 2050**
- Costs largely driven by an aging population, increasing prevalence of CV risk factors, development of novel therapies

Source: Company Reports, Leerink Partners Research, Evaluate, (1) Tandon et al, *World Health Organization*. 2020, (2) Kazi et al, *Circulation*. 2024
EU=European Union, ROW=rest of world, CVD=cardiovascular disease, CV=cardiovascular, CAGR=compound annual growth rate

2 Why Are Pharmas Coming Back to CV? Blockbusters Approaching LOE Cliffs and Rise of Precision Medicine Are Pushing & Pulling Large Pharma to CV

- **With LOEs for Major CV (and non-CV) Drugs of Large Pharma Coming = They Likely Need to Fill These Holes**
  - Current CV blockbusters like **Eliquis, Entresto, Xarelto, and Brilinta face LOEs within the next 5 years**
  - These drugs treat large, blockbuster populations (AFib/VTE for Eliquis, HF for Entresto)
  - Replacing these revenues can be more efficient if: target similar CV populations & "repurpose" field force for new CV agent
  - CV disease remains one of few therapeutic areas with such large chronic populations
- **Unmet need in heart failure remains compelling, which could drive future product launches:**
  - **Best example: Entresto** achieved ~$6B in peak global sales as first-in-class heart failure drug, **surpassing 4 of the 10** listed blockbusters below despite being the newest entrant

Top 10 CV Blockbusters Over Past Four Decades…and their estimated LOEs

Drug	Company	CV Indication	Launch	Mkt Entry	Peak	LOE
Lipitor (atorvastatin)	PFE [MP, Risinger]	Cholesterol-lowering (statin)	1997	5th	$13.1B	2011
Eliquis (apixaban)	PFE/ BMY	Anticoagulant (blood thinner)	2012	3rd	$12.2B	2026
Plavix (clopidogrel)	BMY / Sanofi [OP, Risinger]	Antiplatelet (blood thinner)	1997	2nd	$9.6B	2012
Xarelto (rivaroxaban)	Bayer [Not Rated] / JNJ [OP, Risinger]	Anticoagulant (blood thinner)	2011	2nd	$7.5B	2024
Crestor (rosuvastatin)	AZN	Cholesterol-lowering (statin)	2003	7th	$7.1B	2016
Entresto (sacubitril-valsartan)	NVS	Heart failure (ARNI)	2015	1st	$6.1B	2025
Diovan (valsartan)	NVS	Hypertension (ARB)	1996	2nd	$6.0B	2012
Norvasc (amlodipine)	PFE	Hypertension (CCB)	1992	3rd	$5.3B	2007
Zestril (lisinopril)	AZN	Hypertension (ACE inhibitor)	1987	3rd	$2.4B	2002
Brilinta (ticagrelor)	AZN	Antiplatelet (blood thinner)	2011	3rd	$1.6B	2024

So What's Next?

Expansive Market Potential:

- **CV space presents many new opportunities,** with blockbusters pursuing indications like high cholesterol, anticoagulation, heart failure, antiplatelet therapy, hypertension

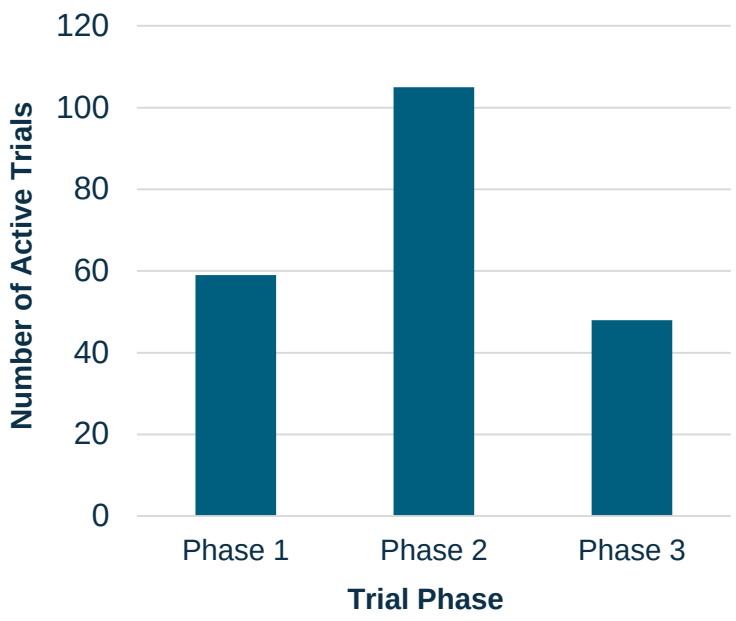
Precision Medicine Driving Future Innovative Therapies:

- **Advances in biotechnology & genetic medicine** enable development of therapies with more precise targets
- This enables design of novel agents that directly address rare CV disorders, **unlocking opportunities in new markets**

Source: Company Reports, Leerink Partners Research, Evaluate, (1) Reed, *Evaluate Vantage*. 2021; SGLT2i=sodium glucose like transporter 2 inhibitor, ARNI=angiotensin receptor-neprilysin inhibitor, ACE=angiotensin converting enzyme, CCB=calcium channel blocker, ARB=angiotensin receptor blocker, LOE=loss of exclusivity

2 Why Are Pharmas Coming Back to CV? Clinical Trials Driving Innovation and M&A Deals Have Been on the Rise in the Last Decade

Active Cardiovascular Clinical Trials (Ph.1 - Ph.3)



- **Per ClinicalTrials.gov statistics…**
  - The total # of active registered CV trials (incl. clinical, preclinical, and academic trials) **grew from <1000 in 2005 to ~9000 trials by 2024**
- **Factors behind increase in CV trials:** 1) Greater emphasis on evidence-based medicine, 2) Increasing funding for CV research 3) Regulatory requirements for registration trials
- Cardiology has seen particular growth in trials for: **heart failure, atrial fibrillation, & structural heart disease interventions**

Select High Premium Cardiology M&A Deals

Acquirer	Target	Year	Total Value	Approx. Premium	Sector	Category
JNJ	Actelion	2017	$30B	23%	Biotech	**Out***
JNJ	Abiomed	2022	$16.6B	51%	MedTech	**Out***
BMY	MyoKardia	2020	$13.1B	61%	Biotech	**Entrenched**
NVS	The Medicines Company	2019	$9.7B	45%	Biotech	**Entrenched**
AZN	CinCor	2023	$1.8B	206%	Biotech	**Emerging**
AMGN	Dezima Pharma	2015	$1.6B	-	Biotech	**Entrenched**

Emerging: Companies newly entering or expanding their presence in the cardiovascular therapeutic space
Entrenched: Companies with a strong, established presence in the cardiovascular therapeutic space
Out: Companies that have exited the cardiovascular therapeutic space

- **Lead Asset Impact:**
  - Mavacamten, for HCM = driver of BMS/MyoKardia deal
  - Inclisiran, for ASCVD & FH = driver of NVS/Medicines Company deal
  - Opsumit/Uptravi/Tracleer, for PAH = driver of JNJ/Actelion deal
- **Higher Premium for Early Stage:** While most assets in M&A were Ph.3 or approved, CinCor is solid precedent for higher premium from emerging player
- **Blockbuster Potential:** CV space continues to offer significant market opportunities, with several M&A drugs projected to achieve >$1B peak

Source: Company Reports, Leerink Partners Research, Evaluate, Biomedtracker, IQVIA; CV=cardiovascular
* JNJ exited the CV space on the therapeutics side, indicating a shift in its focus. For more information see HERE

2 Why Are Pharmas Coming Back to CV? Draw of CV Franchise Evolution Motivates Prior Pharma Leaders in CV to Reinvest Through Novel Approaches

- **Companies with successful current CV franchises** (NVS-Entresto, AZ-Farxiga) are reinvesting in the space
- **New modalities** (siRNA – Leqvio, PCSK9 mAbs) have brough some companies back to the CV sector
- **Recent success of NOACs** (particularly Eliquis) demonstrates continued blockbuster potential in CV space
- **Pipeline diversity** reflects new efforts & multiple paths to keep foothold in large CV space, including more rare CV indications
- **Large obesity players will look for adjacencies** as new "green field opportunities" as obesity gets more crowded

Constant Evolution CV Portfolios for Multiple Pharmas Over Time

Pharma	1990s Portfolio	2000-2010 Portfolio	2010-Present Portfolio	Future Portfolio 2025+
Pfizer	**Norvasc** (CCB, ~$4.9B) **Cardura** (α-blocker, ~$800M)	**Lipitor** (Statin, ~$13B)	**Eliquis** (NOAC, ~$900M) *Partnership with BMS **Vyndamax** (~$3.3B, ATTR-CM)	**Ponsegromab** (GDF-15, Heart Failure) **PF-328948** (Heart Failure)
BMS	**Capoten** (ACE-I, ~$2B)	**Plavix** (P2Y12, ~$7B) **Pravachol** (Statin, ~$2B)	**Eliquis** (NOAC, ~$13.5B)	**Camzyos** (CMI, HCM) **MYK-224** (CMI, HFpEF) **Milvexian** (FXIa, ACS, AF, stroke)
Novartis	**Diovan** (ARB, ~$6B)	**Exforge** (CCB/ARB, ~$1B)	**Entresto** (ARNI, ~$7.5B) **Leqvio** (siRNA, ~$2B+ projected)	**Pelacarsen** (Lp(a), CVRR) **DFV890** (CVRR) **Abelacimab** (Factor XI, stroke)
AstraZeneca	**Zestril** (ACE-I, ~$1.5B) **Plendil** (CCB, ~$1B)	**Crestor** (Statin, ~$7B) **Brilinta** (P2Y12, ~$1.5B)	**Farxiga** (SGLT2, ~$4B+)	**Waiuna** (ATTR-CM) **AZD0870** (oral PCSK9i) **AZD3427** (Heart Failure) **YS2302018** (Lp(a), CVRR)
Merck	**Zocor** (Statin, $5B) **Vasotec** (ACE-I, $2B)	**Zetia** (NPC1L1i, ~$4B) **Vytorin** (Combo, ~$2B)	**Verquvo** (sGCS, ~$1B proj)	**Winrevair** (activin, PH) **MK-0616** (oral PCSK9i, CVRR) **MK-5475** (sGC, PH-COPD)
Sanofi	**Plavix** (P2Y12i, $3.5B) *Partnership with BMS	**Multaq** (AAD, ~$500M)	**Praluent** (PCSK9i, ~$1B)	**SAR447537** (A1-antitrypsin deficiency)

Source: Company Reports, Leerink Partners Research; Evaluate Pharma
See Page 22 for abbreviations

3 What Is Pharma's Commercial Strategy in CV? Movement from "Brute Force" Primary Care Launches to More Targeted Specialty Cardiology Launches

Traditional Approach: Primary Care Focus	Modern Approach: Specialty Cardiology Focus
▪ **Broad, Field-Heavy Deployment**	▪ **Targeted, Specialty-Focused Approach**
▪ **Large Field Force:** ▪ Significant investment ▪ Large, national field teams ▪ "Numbers game" to activate primary care providers	▪ **More efficient, Specialized Teams:** ▪ Leaner field teams focused on specialists ▪ Higher scientific expertise to engage cardiologists
▪ **Mass Advertising:** ▪ High budgets allocated to direct-to-consumer and physician-targeted ads ▪ "Invest to drive patients to office" maximizing reach	▪ **Digital and Precision Marketing:** ▪ Emphasis on digital outreach ▪ Targeting cardiology networks and thought leaders through scientific channels
▪ **Broad Prescription Goals:** ▪ Encouraging use across large patient populations ▪ Focus on common, well-known conditions by generalist doctors (e.g., hypertension, cholesterol)	▪ **Specific, High-Risk Populations:** ▪ Focus on patients with more complex or specific conditions (e.g., HF, HCM) ▪ Treatments require precision, which can lead to improved patient outcomes
▪ **Examples:** ▪ **Lipitor (Pfizer):** Large-scale, broad PCP-targeted campaigns to establish it as a leading cholesterol treatment ▪ **Tenormin (AstraZeneca):** Widespread use in hypertension through mass advertising	▪ **Examples:** ▪ **Leqvio (Novartis):** Focuses on patients with hypercholesterolemia under strict monitoring by specialists ▪ **Camzyos (BMS):** Designed for HCM patients, marketed to cardiologists with REMS requirements

Source: Company Reports, Leerink Partners Research
See Page 22 for abbreviations

4 **What's the Biggest Hurdle in CV?** Historically, Pivotal & CV Outcomes Trials (CVOTs) Are "Bigger Lift," but It's Improving Over Time

Trial design

Standard designs require larger registrational trials:

- Two moderately sized, well-controlled trials
- One large, multicenter trial with robust results

FDA has demonstrated more flexibility in approving certain CV drugs based on a single pivotal trial

- Entresto
- Xarelto
- Repatha

Regulatory Landscape

Real-World Evidence in CV Drug Approvals Can Help

- The FDA approved Entresto for HFpEF based on real-world evidence and clinical trials

Focus on Patient-Reported Outcomes in CV Trials:

- Integrating patient-reported outcomes like KCCQ in clinical trials could provide a more comprehensive evaluation

Phase 2 → Phase 3

Success Rates and Risk Assessment

- Recent studies as of 2021 have shown CV drugs have a ~63% probability of success (POS) in Ph.2 and ~55% POS in Ph.3

Financial Implications:

- Investment requirements increase substantially from Ph.2 to Ph.3 in CV trials, with average costs rising from ~$20M to ~$160M

Key takeaways:

- The CV drug development landscape is evolving towards more flexible and efficient approaches, with regulatory bodies demonstrating openness to innovative trial designs, real-world evidence, and single pivotal trial approvals in cases of significant unmet need
- Transition from Ph.2 to Ph.3 in CV drug development represents a key decision point, combining timely financial & strategic choices

Source: Company Reports, Leerink Partners Research, (1) Yancy, *Circulation*. 2017, (2) McMurray, *European Heart Journal.* 2021
HFpEF=heart failure with preserved ejection fraction, KCCQ= Kansas City Cardiac Questionnaire, CV=cardiovascular

4 What's the Biggest Hurdle in CV? Emerging Industry Trends Could Alleviate Historical Hurdles and Improve Overall Clinical Development in Cardiology

Cardiovascular trials are rapidly evolving through innovative therapies & technological advancements	
Cardiovascular development landscape is experiencing unprecedented growth, with **~9K** ongoing clinical, preclinical, & academic trials adding to CV knowledge base	▪ Sheer breadth of cardiovascular disease spans many conditions: heart failure, coronary artery disease, etc. ▪ Ongoing discovery and rising incidence of cardiovascular conditions / comorbidities fuels increase in CV trials
Precision medicine is reshaping CV treatments with more focus on genetic markers, **moving away from "one-size-fits-all"** to more effective therapies that are easier to study	▪ May lead to enhanced treatment efficacy with more specific drug targets ▪ Could minimize side effects across diverse CV conditions
Strategic selection of composite endpoints in CV trials could streamline clinical and capital efficiency of running larger trials, further attracting large pharma	▪ Achievement of positive Ph. 2 data with efficient trial design and/or strong Ph. 2b results with clear path to pivotal trials can be an attractive strategy for CV-focused companies
CVOTs have become more streamlined with better drug selection and optimized design which could help in meeting payer demands for outcome-based coverage	▪ Supports payers' desire for outcome-based data ▪ Enhanced drug selection, trial design, and patient enrollment can increase likelihood of successful outcomes
Collaboration is growing & intensifying between academia, industry, and regulatory bodies, which could "smooth the path" for CV development and innovation	▪ Fosters more streamlined innovation, drug development, and addressing complex challenges in cardiology medicine ▪ Can accelerate translation of discovery into clinical practice

Key takeaways:

- **Shift towards adaptive trials and real-world evidence enables more flexible, cost-effective studies that better reflect diverse populations**
- **Emerging biomarkers and imaging technologies are revolutionizing patient stratification & endpoint assessment in cardiovascular trials, potentially reducing trial durations and sample sizes**

Source: Company Reports, Leerink Partners Research, (1) Ramasubbu et al, *Advances in Therapy.* 2023, (2) Kosiborod, *Journal of the American College of Cardiology.* 2022

5 **What Are Targets of Interest Right Now?** Mix of "Renaissance" and "Novel" Targets Present Diverse Opportunities in Cardiovascular Drug Development

RENAISSANCE TARGETS*					
Target	**Prior Historical Focus**	**Cardiac Rediscovery**	**Key Differentiation**	**Therapeutic Potential**	**Example Clinical Stage Companies***
CAMKII	Neuronal plasticity & learning	Critical role in cardiac calcium handling	Dual regulation of SR calcium & ion channels	Arrhythmias & heart failure	Cardurion (private)
PDE9	CNS disorders & cognitive function	Heart failure (HFrEF / HFpEF)	Highly specific cGMP degradation independent of NO pathway	Cardiac remodeling and diastolic dysfunction	Cardurion (private)
Lp(a)	Initial genetic risk factor studies	Rediscovered as causal CV risk factor	Distinct from traditional lipid pathways	ASCVD risk reduction & aortic stenosis	Amgen (AMGN), Novartis (NVS), Lilly LLY), Silence (SLN)
MR	Blood pressure & fluid balance	Tissue-specific inflammatory effects	Non-canonical signaling in cardiac tissue	Diabetic cardiomyopathy and heart failure	Bayer (BAYRY), Merck (MRK)
S1P Receptor Modulators	Multiple sclerosis & immune modulation	Cardiac fibrosis & remodeling	Tissue-specific receptor subtype expression	Cardiac inflammation reduction & function improvement	BMS (BMY)
SGLT2	Diabetes therapy	Metabolic regulation in cardiac tissue	Myocardial energy substrate utilization	Heart failure with both preserved and reduced ejection fraction	AstraZeneca (AZN), Boehringer Ingelheim (private)
Factor XI	Coagulation cascade	Thrombosis prevention with reduced bleeding risk	Selective inhibition of intrinsic coagulation pathway	Cardiovascular & venous thromboembolism prevention	BMS (BMY), Bayer (BAYRY), Novartis (NVS)

Source: Company Reports, Leerink Partners Research, *note: list not exhaustive
See Page 22 for abbreviations

5 **What Are Targets of Interest Right Now?** Mix of "Renaissance" and "Novel" Targets Present Diverse Opportunities in Cardiovascular Drug Development

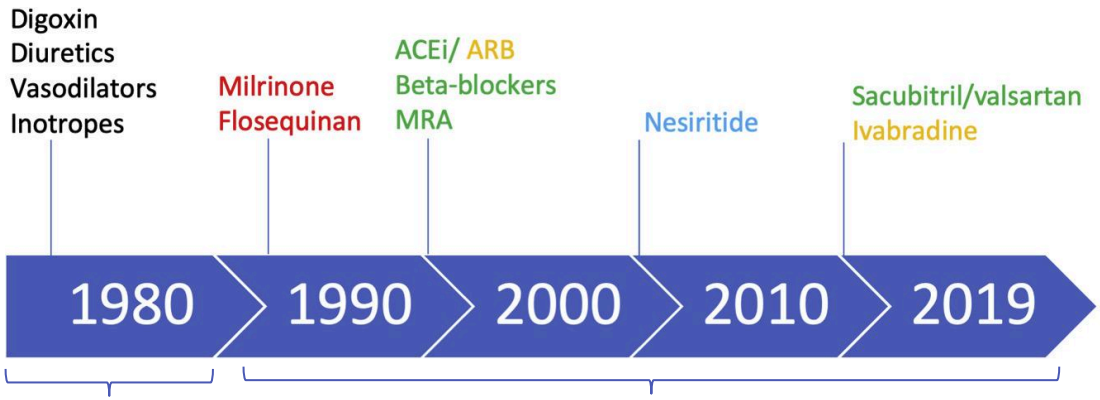
NOVEL TARGETS*					
Target	**Initial Focus**	**Current Development**	**Key Differentiation**	**Therapeutic Potential**	**Example Clinical Stage Companies***
APJ Receptor	Protein processing and lipid metabolism	Enhance Cardiac Function	Improved output with minimal heart rate change	Cardiomyopathy	Bristol Myers Squibb (BMY)
PARP	Cancer therapy	Cardioprotection during ischemia	NAD+ metabolism & energy balance	Acute cardiac injury and MI prevention	AbbVie (ABBV) [OP, Risinger], Pfizer (PFE)
ANGPTL3	Lipid metabolism	Triglyceride and cholesterol regulation	Multi-lipid reduction mechanism	ASCVD risk reduction and metabolic disorders	Regeneron (REGN) [OP, Risinger], Arrowhead (ARWR), Ionis (IONS)
ANGPTL4	Lipid metabolism and glucose homeostasis	Post-prandial lipid handling	Tissue-specific metabolic regulation	Dyslipidemia and metabolic syndrome	Alnylam (ALNY) [MP, Foroohar], Regeneron (REGN), Marea (private)
Angiotensin Receptor (AT)	Blood pressure regulation	Novel targeting approaches (ASO, siRNA)	Extended duration of action with reduced dosing frequency	Treatment-resistant hypertension and cardiorenal protection	Kardigan (private), Alnylam (ALNY), Ionis (IONS)

Source: Company Reports, Leerink Partners Research, *note: list not exhaustive
See Page 22 for abbreviations

6 What Does 2019 FDA Draft Guidance Mean for HF Drug Development?

More focus on symptoms/functional improvement over survival & hospitalization

Timeline of Approved Drugs to Treat Heart Failure



In 1980s, drugs in HF were initially approved without outcomes data

After ~1990s, HF drugs required CV outcomes studies for approval

"Modern" FDA view suggests new HF drug development should include a focus on symptom, QoL, & functional benefits

BEFORE New 2019 FDA Draft Guidance :

- There was a decline in discovery of novel pathophysiologic pathways & new molecular targets
- Hence, saw a drop in pharma investment in HF therapy, in part due to perceived emphasis on need for CV outcomes for approval
- Most drugs were approved for reducing hospitalization & mortality

AFTER New 2019 FDA Draft Guidance, Reflecting "Modern" FDA view

- Suggests improving symptoms or physical function can be a reasonable basis for approving new drugs to treat HF

Why Does 2019 FDA Draft Guidance Matter for Future HF Drug Development?

1. Reflects FDA's favorable thinking regarding **importance** of drugs that improve symptoms & physical function in HF
2. Could help **stimulate development** of novel HF drugs, and **accelerate availability** of novel agents that improve symptoms & physical function
3. Greater focus on showing symptomatic & functional benefits could **improve speed & efficiency** of drug development
4. Improvements in symptoms, physical function, or QoL are **now "opened up" as potentially approvable endpoints** for new HF drugs
5. Creates **more optionality** for biotechs and pharma to pursue HF

Source: Company Reports, Leerink Partners Research. FDA Draft Guidance - Treatment for Heart Failure: Endpoints for Drug Development [LINK], Fiuzat et al. JACC HF. 2020
AHF=acute heart failure, HFrEF=heart failure with reduced ejection fraction, QoL=quality of life

6 What Does 2019 FDA Draft Guidance Mean for HF Drug Development?

More focus on symptoms/functional improvement over survival & hospitalization

Purpose of 2019 Draft Guidance:

1) **To "*make it clear*" that an effect on symptoms or physical function, without a favorable effect on survival or risk of hospitalization, can be a basis for approving drugs to treat HF**
2) To provide recommendations to sponsors on need to assess mortality effects of drugs in development to treat HF

FDA's Thinking on Symptoms & Functional Improvement – Positive Quotes or Guidance Insights	
Symptom & functional benefits seen as valuable	▪ "*A drug that improves symptoms or function when added to standard of care would be valuable even if it did not improve survival or hospitalization*"
Symptom & functional benefits may outweigh lower survival	▪ "*If a drug provided substantial and persistent improvement in symptoms or function, especially for patients with NYHA Class III or IV HF, some decrease in survival would be acceptable*"
Evidence of effectiveness	▪ Could be based on improvements in symptoms (e.g., dyspnea, fatigue, edema) and/or function (e.g., walking, exercising, performing other activities of daily living)
Endpoints acceptable to FDA	▪ Individual symptoms or a composite symptom score, exercise capacity, functional capacity, NYHA functional class, and measures of activity/daily living (i.e., KCCQ & MLHFQ are commonly used & validated endpoints)
FDA willing to consider novel endpoints	▪ Other clinical outcome assessments, other measures of functional capacity, and measures of daily activity (e.g., accelerometry data)

Source: Company Reports, Leerink Partners Research. FDA Draft Guidance - Treatment for Heart Failure: Endpoints for Drug Development [LINK], Fiuzat et al. JACC HF. 2020

HF=heart failure, MoA=mechanism of action, Tx=treatment, KCCQ=Kansas City Cardiomyopathy Questionnaire, MLHFQ=Minnesota Living with Heart Failure Questionnaire, NYHA=New York Heart Association

6 What Does 2019 FDA Draft Guidance Mean for HF Drug Development?

More focus on symptoms/functional improvement over survival & hospitalization

Purpose of 2019 Draft Guidance:

1) To "make it clear" that an effect on symptoms or physical function, without a favorable effect on survival or risk of hospitalization, can be a basis for approving drugs to treat HF
2) **To provide recommendations to sponsors on need to assess mortality effects of drugs in development to treat HF**

FDA's Thinking on Need for Mortality Data

- **Mortality might still be important as a safety measure** – If a drug does not show an improvement in morbidity or mortality endpoints but improves feeling or function, morbidity & mortality should be considered to evaluate safety, and provide reasonable assurance that the drug did not increase mortality
- **When approval is based on improvement of symptoms or function –** FDA will consider the following factors in determining whether & when (i.e., pre- or post-approval) additional mortality data are needed:
    1. Mortality & other safety findings of pharmacologically similar drugs (i.e., safety of new drug in a class with established safety could be supported by existing data, but drugs with novel MoA's are more likely to require mortality data)
    2. Planned duration of exposure (i.e., no long-term mortality data needed for shorter-term Tx's <10 days)
    3. Mortality & other safety findings of the drug in a closely related population (i.e., in which at least a subset of the patients had heart failure or were at risk of heart failure)

Source: Company Reports, Leerink Partners Research. FDA Draft Guidance - Treatment for Heart Failure: Endpoints for Drug Development [LINK], Fiuzat et al. JACC HF. 2020
HF=heart failure, MoA=mechanism of action, Tx=treatment.

7 CV Case Studies: Key Learnings from NAMS's Obicetrapib & BMY's Camzyos

NewAmsterdam (NAMS)	Bristol Myers (BMY)
Drug - Obicetrapib (oral CETPi)	**Drug - Camzyos (CMI)**
Indication - CV risk reduction / LDL-C lowering	**Indication - Obstructive HCM**
▪ **Strategic approach to clinical data at launch** ▪ **Dual-Purpose Data Generation:** Leveraging NDA review period for simultaneous CVOT data collection maximizes operational efficiency, timing, & positioning ▪ **Commercial & clinical advantages** ▪ **Accelerated Market Presence:** Parallel tracking of approval and outcomes data allows faster market entry while building comprehensive evidence base ▪ **Appeal to Multiple Stakeholders:** Early outcomes data strategically addresses: ▪ Cardiologist adoption ▪ Value proposition for favorable payer coverage ▪ Regulatory requirements for long-term safety ▪ **Strategic Value Drivers** ▪ **Competitive Differentiation:** early outcomes data distinguishes obicetrapib in the CVRR landscape ▪ **De-risked Development:** Fully funded CVOT program ensures uninterrupted data generation & focused commercial execution ▪ **Market Leadership:** Proactive outcomes data strategy positions obicetrapib for rapid uptake in a high-value CV market segment	▪ **REMS Impact on Commercial Execution** ▪ **Operational Complexity:** Multi-layered REMS protocol requiring echo monitoring & stakeholder certification requirements create significant barriers ▪ **Practice-Level Implementation Challenges:** Limited REMS-certified physicians per practice (often 1:10 ratio) creates logistic bottlenecks & reduces access ▪ **Market Development Dynamics** ▪ **Building A New Market:** BMY's pioneering position in HCM required substantial investment in: ▪ Driving disease awareness ▪ Understanding treatment paradigm ▪ Healthcare provider education ▪ **Strategic Market Evolution** ▪ **Segmentation of Risk Factors:** REMS requirements represent Camzyos-specific challenges rather than HCM market barriers, creating opportunities for differentiated market entrants ▪ **Next-Gen Positioning:** ▪ CYTK/aficamten's improved cardiac safety & minimal LVEF reduction suggest possibly less restrictive REMS or monitoring requirements ▪ EWTX[OP, Schwartz]/EDG-7500's prelim. efficacy without significant EF impact suggest potential for streamlined adoption in oHCM, nHCM (and potentially HFpEF)

Source: Company Reports, Leerink Partners Research
See Page 22 for abbreviations

8 Decoding Cardiology Clinical Trial Endpoints: Select Endpoints to Watch for With Example Catalysts of Where They Mattered

Efficacy Endpoint	Technical definition	What it means	Indication	"Bar for success"	Historical catalyst
MACE	Composite of CV death, MI, and stroke	Measure of significant CV events	Lipid lowering, CV disease prevention	**~15-20% reduction**	Ph. 3 JUPITER (Crestor) [LINK]
6MWD	Submaximal exercise test for functional capacity	Distance walked in 6 minutes	PAH, heart failure, respiratory diseases	**30-50 meter improvement**	Ph. 3 STELLAR (Winrevair) [LINK]
NYHA Class Change	Subjective measure of heart failure impact	Change in heart failure patient classification	Heart failure, cardiomyopathies (i.e., HCM, Fabry's, Gaucher's)	**≥1 class improvement**	Ph. 3 PARADIGM-HF (Entresto) [LINK]
KCCQ	23-item questionnaire on physical limitations, symptoms, QoL	Patient-reported heart failure measure	Heart failure, cardiomyopathies (i.e., HCM, Fabry's, Gaucher's)	**5-point improvement**	Ph. 3 EMPEROR-Preserved (Jardiance) [LINK]
LVEF	% of blood leaving heart during each contraction	Measure of left ventricle pumping	Heart failure, cardiomyopathies (i.e., HCM, Fabry's, Gaucher's)	**5% improvement**	Ph. 3 SOLVD (Vasotec) [LINK]
pVO2	Max oxygen consumption during exercise	Measure of cardiorespiratory fitness	Heart failure, cardiomyopathies (i.e., HCM, Fabry's, Gaucher's)	**1-2 mL/kg/min increase**	Ph. 3 SEQUOIA (aficamten) [LINK]

On average, MACE trials can take 3-5 years to complete

LVEF & pVO2 are quantitative, physiological measures less susceptible to patient or observer bias

Key Upcoming Catalysts

MACE
- Ph. 3 PREVAIL (obicetrapib)
  - *2H26*
- Ph. 3 HORIZON (pelacarsen)
  - *2026*

KCCQ
- Ph. 3 SONATA (sotagliflozin)
  - *Early 2027 (our est.)*
- Ph. 3 ACACIA (aficamten)
  - *2026 (our est.)*
- Ph. 3 ODYSSEY (mavacamten)
  - *2Q25*

pVO2
- Ph. 3 MAPLE (aficamten)
  - *1H25*

Key takeaways:

- CV endpoints are **well-established, validated, and specific** to different disease processes, with **MACE** standing out as a universally accepted key endpoint applicable across all cardiac disease indications
- We see increasing emphasis on **outcomes trials** in CV drug development, reflecting a shift towards demonstrating real-world patient benefits and long-term efficacy, which is crucial for regulatory approval and market success

Source: Company Reports, Leerink Partners Research, Evaluate, Biomedtracker, Clinicaltrials.gov, (1) Packer et al. *New England Journal of Medicine*. 1991

MACE=major adverse cardiac event, 6MWD=6-minute walk distance, MI=Myocardial Infarction, PAH=Pulmonary Arterial Hypertension, NYHA=New York Heart Association, KCCQ=Kansas City Cardiomyopathy Questionnaire, QoL=Quality of Life, LVEF=Left Ventricular Ejection Fraction, pVO2=Peak Oxygen Consumption, HCM=hypertrophic cardiomyopathy

Acronym & Abbreviation Master List

- **AAD -** antiarrhythmic drug
- **ACEi -** angiotensin-converting enzyme inhibitor
- **ACS** - acute coronary syndrome
- **Angptl3**: Angiopoietin-like protein 3
- **Angptl4**: Angiopoietin-like protein 4
- **ASCVD -** Atherosclerotic cardiovascular disease
- **AFib** - Atrial Fibrillation
- **ARB** - Angiotensin Receptor Blocker
- **ARNI** - Angiotensin Receptor-Neprilysin Inhibitor
- **ASO**: Antisense Oligonucleotide
- **APJ –** Apelin Receptor
- **ATTR-CM -** Transthyretin amyloid cardiomyopathy
- **AT**: Angiotensin
- **CAMKII** - Calcium/Calmodulin-Dependent Protein Kinase II
- **CCB -** Calcium channel blocker
- **CMI** - cardiac myosin inhibitor
- **CNS** - central nervous system
- **CVOT** - Cardiovascular Outcomes Trial
- **CVRR** - Cardiovascular risk reduction
- **cGMP** - Cyclic guanosine monophosphate
- **Echo** - echocardiogram
- **FH** - familial hypercholesterolemia
- **FXIa** - factor XI (FXIa) inhibitor
- **GPCR** - G protein-coupled receptors
- **GRK5** - G Protein-Coupled Receptor Kinase 5
- **GRK2**: G protein-coupled Receptor Kinase 2
- **HCM** - Hypertrophic Cardiomyopathy
- **HFpEF** - Heart Failure with Preserved Ejection Fraction
- **hsCRP** - High-Sensitivity C-Reactive Protein
- **KCCQ** - Kansas City Cardiac Questionnaire
- **Lp(a)** - Lipoprotein (a)
- **mAbs** - Monoclonal Antibodies
- **MI –** myocardial infarction
- **MR** - Mineralocorticoid Receptor
- **NAD+ -** Nicotinamide adenine dinucleotide
- **NO** - nitric oxide pathway
- **NOAC** - Non-Vitamin K Antagonist Oral Anticoagulant
- **NPC1L1i -** Niemann-Pick C1-like 1
- **nHCM** - Non-Obstructive Hypertrophic Cardiomyopathy
- **oHCM** - Obstructive Hypertrophic Cardiomyopathy
- **PARP** - Poly (ADP-Ribose) Polymerase
- **PDE9** - Phosphodiesterase 9
- **PCSK7** - Proprotein Convertase Subtilisin/Kexin Type 7
- **PCSK9** - Proprotein Convertase Subtilisin/Kexin Type 9
- **P2Y12i** - purinergic signaling receptor Y12
- **PH** - pulmonary hypertension
- **REMS** - Risk Evaluation and Mitigation Strategy
- **siRNA** - Small Interfering RNA
- **S1P Receptor Modulators** - Sphingosine-1-Phosphate Receptor Modulators
- **SGLT2i** - Sodium-Glucose Cotransporter 2 Inhibitor
- **sGCS** - Soluble Guanylate Cyclase stimulators
- **SR** - sarcoplasmic reticulum

Disclosures Appendix

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Analyst Certification

I, Roanna Ruiz, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

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			IB Serv./Past 12 Mos.	
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HOLD [MP]	76	25.6	14	18.4
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