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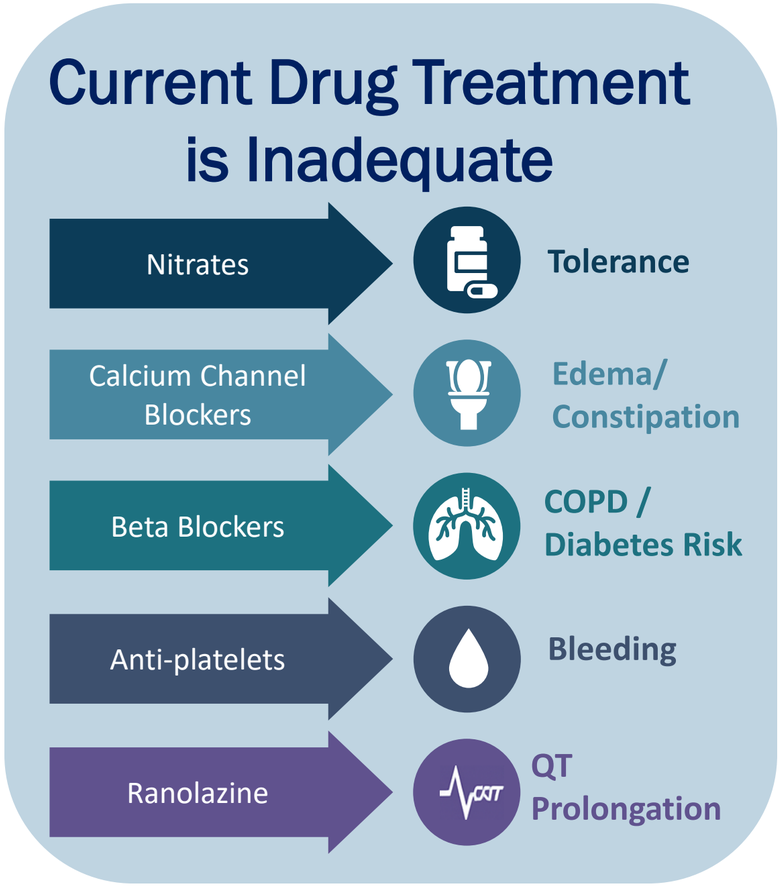
Revolutionary Therapy for Refractory Angina in Coronary Artery Disease

John F. Schmedtje Jr., MD
Roanoke, Virginia

Coronary Artery Disease /Angina Pectoris
The Pharmaceutical Standard of Care for Angina has Severe Limitations & Gaps



A New Treatment for Angina Pectoris Represents a Significant Opportunity Within $16 Billion Global Market by 2029

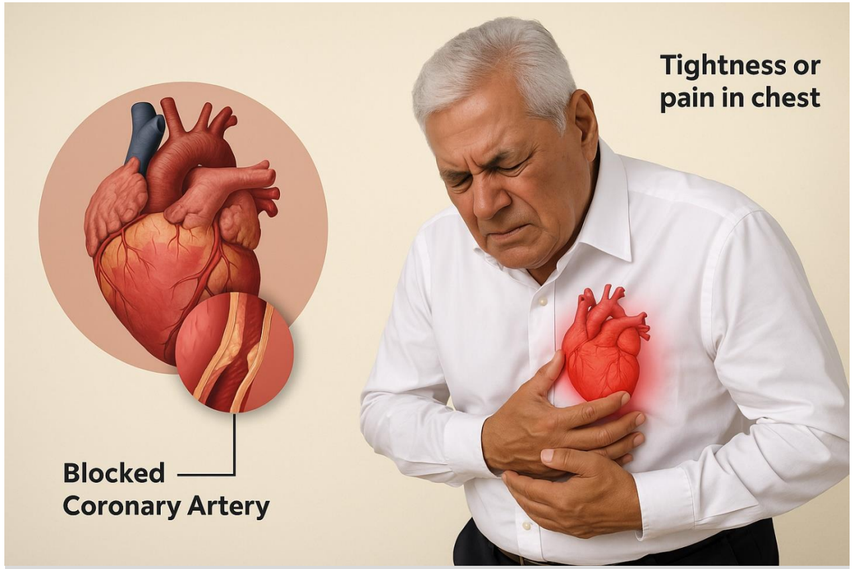
21% of
Angina patients have a monthly attack

10 million
Angina patients in US

Annual mortality
3% to 17%

Invasive Procedures Delay the Inevitable: New Drugs are Needed

Our Solution Features A Dual-Action Mechanism: *Not Just Another Nitrate*



Hypoxia & Inflammation are Key Factors in Angina Pectoris

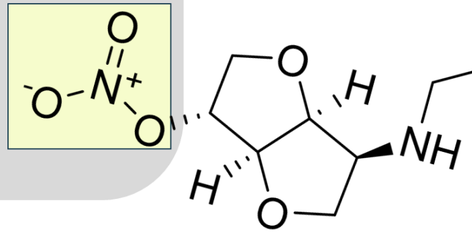
- **Hypoxia leads to triggering of neuronal afferents and increased expression of inflammatory cyclooxygenase-2**
- **Hypoxia and inflammation in heart diseases with different etiologies may be reversed by the same molecule: Nitric Oxide (NO), released by Nitroglycerin and Isosorbide Nitrates**

Schmedtje et al. J. Biol. Chem. 1997;272:601-608.
Schmedtje et al. Biomed. Pharmacother. 2024;173:116378.

CR-0305 is Designed to Deliver a ONE-TWO Punch

ONE

Nitrate donates NO (nitric oxide) to quickly dilate arteries and provide immediate relief by reversing hypoxia



TWO

Glycolamide (urea analog) **facilitates NO formation by the cell itself**

CR-0305 uniquely offers both immediate vasodilation (rapid NO donation) and potential long-term vascular benefit (cellular NO upregulation)

Glycolamide moiety for extended action → potentially overcomes tachyphylaxis plaguing traditional therapies

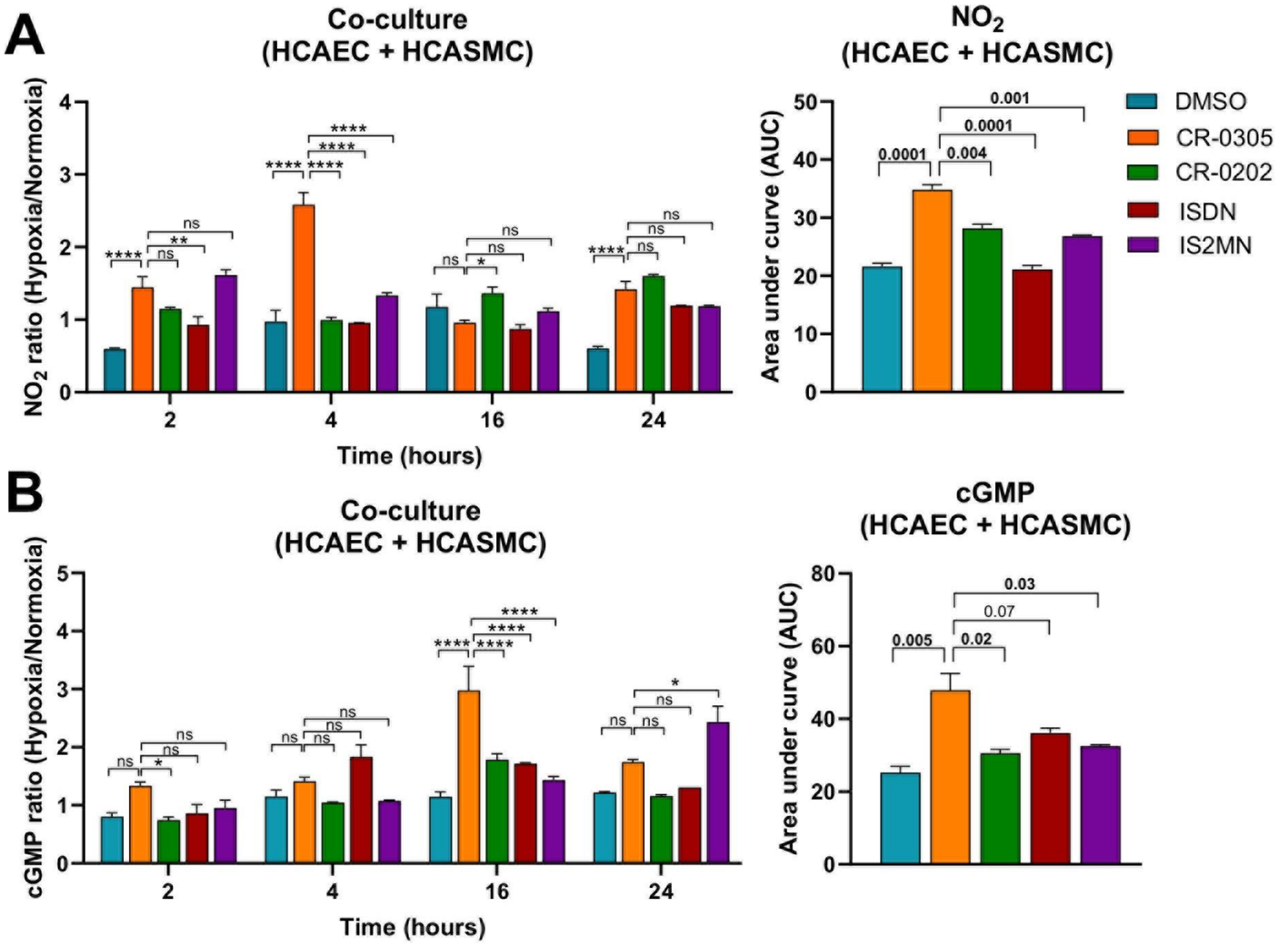
Preclinical data: CR-0305 likely provides durable and superior vasodilation to gold-standard agents and may provide a SELECTIVE effect where hypoxia exists

CR-0305 Boosts Key Vasodilatory Biomarkers in Cellular Hypoxia *In Vitro* New Approach Methodology: Human Coronary Artery in a Dish

New Approach Methodology: Application of CR-0305 to human (HCAEC/HCASMC) cell cultures grown under low-oxygen (hypoxic) conditions produced a significant increase in nitric oxide metabolite (NO_2) and cyclic GMP (cGMP) biomarkers compared with normoxia

A) CR-0305 significantly raised the hypoxia/normoxia ratio of NO_2 over time. Two-way ANOVA with Tukey post-hoc was used to assess statistically significant differences: * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001. Area-under-curve (AUC) analysis confirmed robust and statistically significant induction compared to control, p values listed.

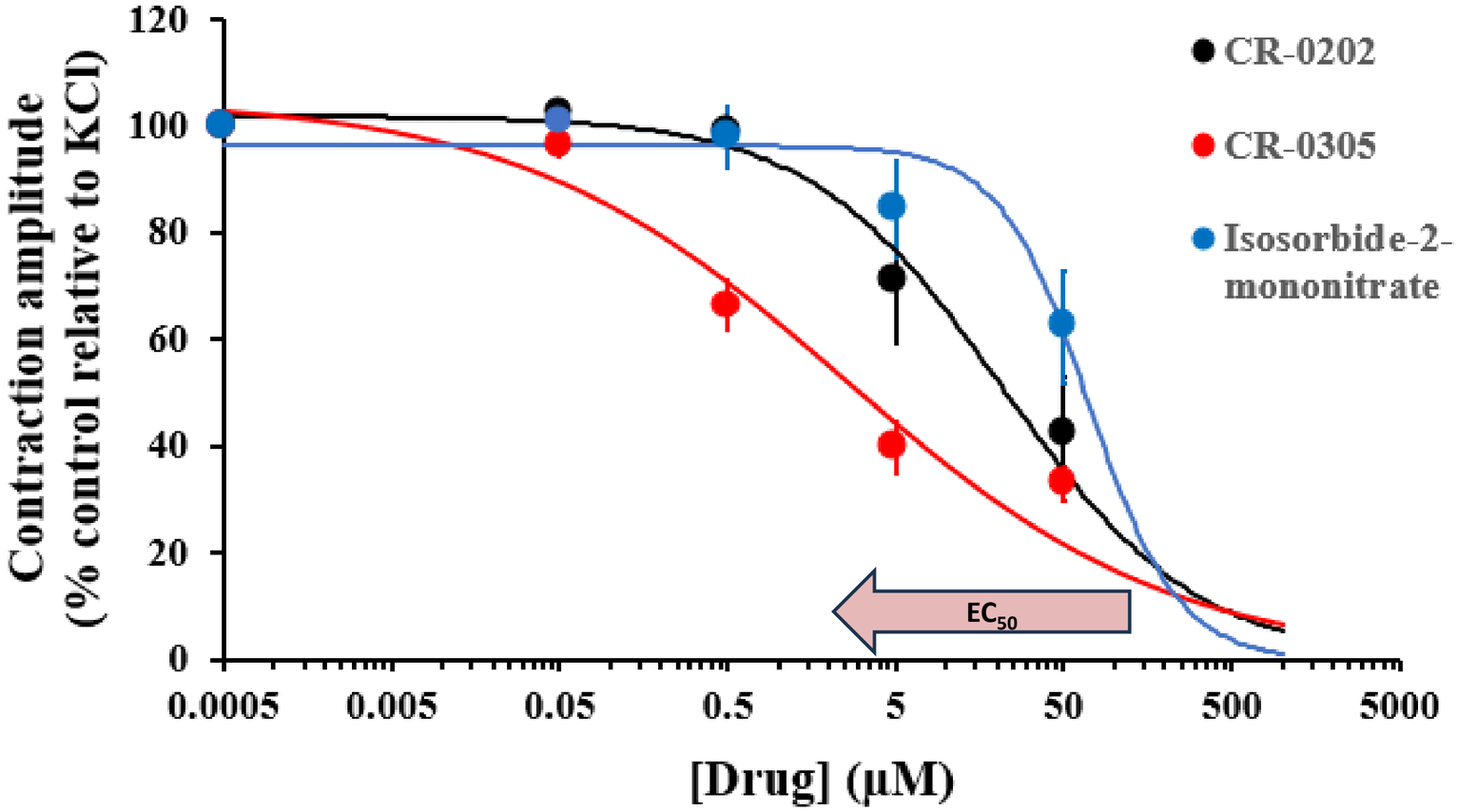
B) Co-culture cell lysates revealed strongly elevated cGMP production, mirroring the NO_2 increase and highlighting CR-0305's powerful dual effect on endothelial function.



CR-0305 Demonstrates Higher Potency than Isosorbide Mononitrate in Human Coronary Arteries *Ex Vivo*

In human coronary arteries *ex vivo*, direct comparison of CR-0305 with a SOC organic nitrate after pre-contraction demonstrates vasorelaxation at much lower concentrations than isosorbide mononitrate

Specifically, CR-0305 achieves half-maximal relaxation (EC_{50}) at **3.0µM**, vs. **67.8µM** for isosorbide mononitrate—making CR-0305 over 20 times more potent. The superior potency suggests the potential to deliver more consistent, effective relief for patients who fail current nitrate therapies.



IP and Team Building Status

Global Patent Portfolio:

Protected under US Patents 10,501,471 (filed June 2019), 10,913,748 (October 2019), and 11,779,560 (March 2021)

Protected by international patent applications through PCT/US2019/058241 (October 2019) and PCT/US2021/024540 (March 2021)

Team Building

CR-0305 is currently undergoing development with Murali Duvvuri and Tilmann Brotz as co-CSOs at PharmaDirections.

Legal guidance is provided by Andrew White and Cathy Zhang of Williams Mullen.

Medicinal chemistry under development in concert with Cayman Chemical Company.

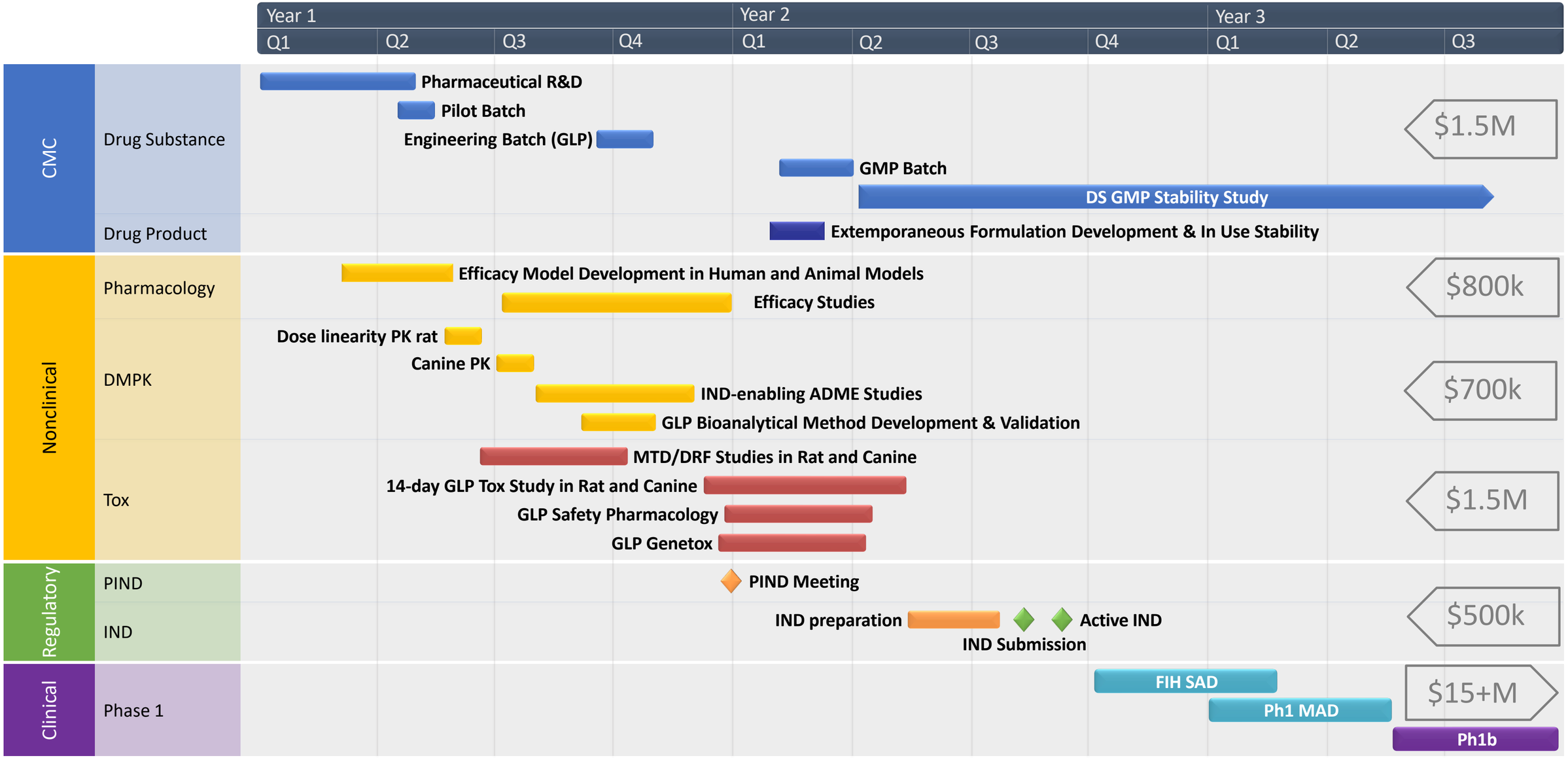
Next Steps

Evaluate CR-0305 in human coronary arteries *ex vivo* and human cell culture *in vitro* to clarify mechanism of action, using NAM

Extend initial studies indicating lack of toxicity to more detailed studies of absorption, distribution, metabolism, and excretion (ADME-TOX) in animal models

Perform *in vivo* proof of concept

CR-0305 Development Timeline



Company Overview - First-in-class therapy for refractory angina pectoris

Urgent Unmet Medical Need

- *Angina pectoris afflicts more than 10 million Americans, with 21% of patients still suffering monthly attacks despite medical therapy. Up to 900,000 patients in the US have the more serious refractory angina, with up to 75,000 new cases each year and annual mortality up to 17%.*
- *INOCA (ischemia with no obstructive arteries) patients are mainly women, and their prognosis is similar to that of patients with single vessel obstructive disease, but there is no option for mechanical revascularization.*
- *Existing treatments such as calcium channel blockers, anti-platelets, nitrates are hampered by insufficient efficacy, frequent tolerance, and significant side effects, leaving a large and underserved population.*

Lead Asset: CR-0305 - Innovative Dual-Mechanism Solution

- *CR-0305 delivers a "one-two punch": rapid vasodilation via nitric oxide (NO) donation and sustained benefit by inducing cellular NO production, designed to achieve relief even where conventional nitrates fail.*
- *Designed to overcome tachyphylaxis (tolerance) by addressing multiple pathways, CR-0305 aims to provide both fast-acting and durable control of angina symptoms.*

Strong Preclinical Data & IP Protection

- *CR-0305 exhibits 23× greater vasodilatory potency than isosorbide mononitrate (IC_{50} 3.0μM vs. 67.8μM) in human coronary artery ex vivo, with significant improvements in NO and cGMP generation using NAM in vitro.*
- *CR-0305 demonstrates low toxicity in human cell studies and secured IP protection, priority date 2019, with US patents granted and global patents pending.*

Clear Path to First-in-Human Trials

- *Over $1.8M secured from NIH SBIR, Virginia CCF, and private investors to date.*
- *Our financial plan requires $5M for ADME-Tox work, NAM proof of concept with in vivo and ex vivo demonstrations of efficacy, leading to pre-IND meeting with the FDA.*
- *Subsequently we will need $15M to complete IND-enabling studies, file IND, and launch first-in-human Phase 1 clinical trials of oral CR-0305.*

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OPENING HEARTS

A Management Strategy for Coronary Artery Disease with CR-0305

Visit: www.coeurative.com

Contact: jfs@coeurative.com